NONTUBERCULOUS DISEASES

OF

THE CHEST

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CHAPTER I

THE PHYSIOLOGY AND PATHOLOGIC PHYSIOLOGY OF RESPIRATION

By G G Ornstein, M D and E H Robitzek, M D

AN EVALUATION of respiratory physiology in the human requires study of an elaborate process whereby reciprocal transport of oxygen from atmosphere to tissues and carbon dioxide in the reverse direction is accomplished Rhythmic thoracic motion, under nervous and humoral control, brings atmospheric air into periodic contact with the alveolar membrane for further transport to distant tissues via the circulating blood The anatomic structures and the physiologic mechanisms involved are so thoroughly integrated that no one can properly be separated and all must therefore be considered under combined and descriptive headings

Thoracic Movements

The essential skeletal framework upon which the thoracic motion is accomplished is composed of the ribs, sternum, the vertebral column and the scapulae The ribs connect posteriorly to the spine through a flexible system of multiple hinges, the costo vertebral joints, and anteriorly to the sternum through the semi flexible costo sternal cartilages Expansion of the skeletal cage occurs on inspiration and is a complex of upward, forward and lateral motions It is accomplished through the contractions of the external intercostal muscles, the scaleni, the pectorals, the serrati and the trapezius and rhomboids Further increase in the capacity of what has been called the thoracic 'bell jar' is obtained by the descent of the diaphragm which exerts most of its thrust in a downward and anterior direction Expiration is fundamentally passive except when the individual is under stress. Then the internal intercostals and the abdominals, facilitated by the abdominal viscera and a relaxed diaphragm, contract to diminish the volume of the thoracic cage The anterior, inferior portions of the thorax are most

expansile, the posterior, apical and apico-mediastinal portions are least so

The lungs follow this scheme of expansion insofar as the essentially non-expansile root zone allows There is relatively unhampered motion in the lung areas situated anteriorly and below the root regions, the apical and posterior areas may descend and come forward and laterally only in accordance with the descent, forward and lateral motion of the lung root This motion is dependent upon a resilient bronchial tree the elasticity of which is derived from its muscular, elastic and cartilagenous components On inspiration the motion is largely one of descent and a "fanning out" with concomitant elongation and widening The reverse occurs on expiration

The role of the diaphragm can scarcely be overemphasized as it relates to the efficacy of overall ventilation Observations on normal subjects and upon pre- and post operative patients by clinical, fluoroscopic and ventilatory studies indicate that satisfactory ventilation is overwhelmingly dependent upon proper diaphragmatic function It is for this reason that surgical procedures for the lower lobes must be planned carefully and as carefully executed in order to preserve the integrity of the diaphragm

The motivating factor in the control of the thoracic movements is the presence of the respiratory center situated in the medulla In addition to its inherent rhythmicity this center is influenced by nervous impulses from the lung parenchyma via the vagus which stimulate deflation on full inspiration and inflation on full expiration (Hering-Breuer reflex) The medullary center is futher stimulated by impulses originating in the cortex, the carotid sinus, the aortic node, the skin, and many peripheral and cranial sensory nerves, the diaphragm and other respiratory muscles Aortic hypertension, acting through receptors in the aortic arch and the carotid sinus causes depression of respiration, the converse is also true Further influence upon the respiratory center is provided by humoral elements, notably carbon dioxide excess, oxygen deficit and acid base alterations Of these, the effect of carbon dioxide is probably most important, the factor of oxygen lack, operating largely through the carotid sinus, is probably the least By virtue, then, of these complicated respiratory movements is the alveolus assured of a constant and adequate supply of oxygen In the phase of inspiration the increased volume of the thoracic cage, in accordance with Boyle's law, reduces the intrathoracic pressure and establishes a gradient which induces an

influx of air from the relatively higher pressured atmosphere In expiration the converse operates

Ventilation

The logical purpose of rhythmical thoracic movements is the provision of atmospheric air into intimate contact with respiratory epithelium and the removal of excess carbon dioxide This process is known as ventilation A number of conventional terms have been utilized and are generally accepted in the description of the ventilatory fractions composing total ventilation

Tidal air This fraction is usually described as the volume of air that is inhaled and exhaled during a single quiet respiratory cycle Values of from 200 to 800 cc in clinically normal individuals reduce the significance of this determination and complicate its interpretation It is important to record the conditions under which any "quiet respiratory cycle" is measured since wide variations obtain, even in the same individual, depending upon whether the subject is basal, recumbent, upright, and emotionally stimulated or depressed The values obtained are found to vary with habitus, with the efficiency of gas exchange and with the chemico circulatory status of the blood In the average man the *tidal air* roughly approximates 500 cc

Complemental air Some authors take the total volume of air that can be inhaled from the beginning of a quiet respiration as the *complemental air* Others begin measurement at the conclusion of a quiet inspiration This volume averages 3000 cc in the former instances, 2500 cc in the latter

Supplemental or reserve air This fraction, averaging about 1000 cc, represents the volume of air which can be forcibly expired following a quiet expiration

Vital capacity The sum of the tidal, complemental and supplemental volumes is known as the vital capacity The average volume usually given is 4000 cc

*Residual air** Following a full forced expiration approximately 1200 cc of air is still present within the lungs This fraction is known

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*Air which is expired is susceptible of easy measurement through the use of any of a number of quantitatively calibrated receptacles Residual air is determined by analysis of a known mixture of gases after a period of rebreathing The dilution method of Van Slyke and Binger is satisfactory More recently greater accuracy has been provided through the use of the oxygen dilution method of Darling *et al* Lung volumes at any phases of respiration may similarly be determined.

as the residual air Included with this volume is the *minimal air* volume which, while present in the alveoli, cannot readily be measured, and the absence of which in atelectasis causes pulmonary tissue to lose its buoyancy It has been found to amount to about 200 cc

Total capacity The total volume of air which the lungs may contain after full inspiration, commonly averaging 5000 cc., is known as the *total capacity*

Midcapacity The quantity of air present within the lungs at the mid point during a quiet respiration is variously known as the *mid capacity, the subtidal volume* and the *functional residual air* Some authors prefer to consider this volume to be more properly measured from the point of expiration after a quiet respiration It thus represents the sum of the supplemental and residual air volumes

Resting minute ventilation The total volume of air ventilated in one minute under conditions of rest is known as the *minute volume* or the *resting minute ventilation* The average minute volume is about 7000 cc but varies from 4000 to 9000 cc in normal individuals. This variability has been amply demonstrated in hundreds of determinations, the factors dictating extreme care in interpretation are those noted under ' tidal air' —of which, in a sense, the resting minute ventilation is a function

Maximum minute ventilation The maximum quantity of air that can be ventilated in one minute under conditions of forced breathing first described by Hermannsen is known as the maximum breathing capacity or maximum minute ventilation It varies widely but averages 154 liters for males and 100 liters for females (Cournand *et al*)

Ventilatory factor The quotient of maximum minute ventilation divided by the resting minute ventilation is known as the ventilatory factor (Ornstein *et al*) Composed as it is of the two moderately variable figures referred to in the preceding two paragraphs, this factor is subject to some fluctuation It is this feature which endows the ventilatory factor with its sensitivity in the early revelation of deficiencies in pulmonary reserve function The average factor is 20 for men and 13 for women Cournand and Richards have utilized these figures in another manner in arriving at their estimate of the *breathing reserve* By expressing the difference between resting and maximal minute ventilations as a per centage of the maximal minute ventilation they obtain the *percentage breathing reserve* The threshold of dyspnoea is usually found in the 60 to 70 per cent range Essentially similar purposes are served by estimations of the ventilatory factors and breathing reserves, the former is a more

nsitive index and less complicated in its derivation In practical usage n arbitrary figure of 6 has been determined as the dividing line between adequate and an inadequate ventilatory factor Major thoracic surgery is ill advised for patients whose performance is below this value

It must be emphasized that all of the above figures are subject to wide variations depending on the height, weight, age, sex, body configuration and state of physical training of any subject The vital capacity retains a fairly well fixed relationship with the surface skin areas of the body and approximates ten volumes of tidal air Measurement of the vital capacity, while a rough estimate of the pulmonary ventilation, gives little information about the pulmonary reserve and none of the gaseous exchange across the respiratory epithelium Thus, an apparently satisfactory vital capacity may be associated with deficient oxygen utilization and an apparently deficient vital capacity with excellent utilization Consideration of the total of each of these factors is required for the proper evaluation of pulmonary efficiency This will be considered in the discussion of pathologic physiology

Gaseous Exchange

We are concerned here principally with gas exchange at the alveolar membrane and in the peripheral capillary bed The catalytic oxidation reduction reactions involved in cellular metabolism are somewhat oblique to this discussion and will not be considered here Our prime interest is in the delivery of oxygen to the tissues and the removal of carbon dioxide

The alveolar membrane constitutes the first barrier to be penetrated It is composed of alveolar epithelium and capillary endothelium and is thereby two cells in thickness That the capillary may be uncovered at some points has been pointed out, in these zones the thickness may be unicellular The membrane has the physical characteristics of any wet membrane Through it gases diffuse in accordance with the laws of partial pressures, their coefficients of solubility and their rates of diffusion Alterations of any of these or alterations in the character or surface of the membrane cause changes in the rate or degree of gaseous exchange On the other side of the membrane is the receptor system, namely, the blood It plays its role of supplying hemoglobin and bicarbonate as vehicles for the transport of oxygen and carbon dioxide respectively Alterations in the rate of blood flow, concentration of hemoglobin or concentration of bicarbonate causes alterations in the gas carrying

capacity of the blood and thereby of the rate and degree of gaseous exchange despite an entirely *competent alveolar membrane*

The importance of the presence of hemoglobin and bicarbonate is revealed upon consideration that partial pressures and coefficients of solubility are responsible for the delivery of gases into fluids in simple solution alone Thus, arterial blood contains 0 24 and 2 5 volumes per cent of oxygen and carbon dioxide respectively in simple solution Venous blood contains 0 1 and 3 0 volumes per cent of oxygen and carbon dioxide Yet the total volumes per cent of oxygen and carbon dioxide in arterial blood are 19 0 and 52 0 respectively and in venous blood the total volumes are 13 0 and 58 0 * *An unstable chemical combination of oxygen with* hemoglobin and bicarbonate with carbon dioxide is responsible for the *difference*

Within the pulmonary capillary the oxyhemoglobin combination is produced and the carbon dioxide bicarbonate combination is disrupted Motivation for this shift stems from the gradient between partial pressures of oxygen and carbon dioxide in alveolar air and venous blood In *alveolar air the oxygen pressure is 130 mm Hg and carbon dioxide exerts* 40 mm Hg In venous blood the oxygen pressure is 40 2 mm Hg , the carbon dioxide pressure is 45 6 mm Hg The dissociation of carbon dioxide is facilitated in the presence of oxygen in an almost quantitative fashion

In the peripheral capillaries essentially the reverse of the above occurs Tissues low in oxygen and high in carbon dioxide concentration create *conditions favoring oxyhemoglobin dissociation A relatively* slight drop in oxyhemoglobin saturation liberates considerable oxygen and this process is greatly facilitated in the presence of a high concentration of carbon dioxide The degree to which oxyhemoglobin dissociates is dependent upon the steepness of the gradient between capillary and tissue oxygen *content* and upon *the rate of flow* through the capillaries Stasis fosters profound hemoglobin reduction The significance of oxygen liberation in the presence of high concentrations

*It is this remarkable affinity of hemoglobin for oxygen that limits the value of arterial blood oxyhemoglobin saturation determinations in the evaluation of lung *function* For significant changes in the levels of saturation to appear anoxia of a degree which is apparent by other simpler methods must be present The oximeter has been devised to overcome this objection It measures hemoglobin saturation *peripherally by* continuous quantitative estimation of color change The delicacy and rapidity with which minute by minute estimations may be made make the oximeter an apparatus of great potential value Its ultimate status has not been determined

of carbon dioxide was emphasized by Bohr and is described in detail in the section devoted to "acapnia"

Mechanism of Cough

This physiological mechanism, occurring so commonly in pathological states involving the tracheo bronchial tree, has essentially two components, the inspiratory phase and the explosive expulsive phase Controlled by a center in the medulla, it may be initiated by sensory points in the pleura, bronchial bifurcations, trachea, larynx, oropharynx, naso pharynx, oesophagus and ear The deep inspiration constituting the first phase terminates with a closure of the glottis and a contraction of the thoracic and abdominal muscles, at this time considerable intrathoracic pressure is created The glottis is then suddenly opened allowing a violent expulsion of air This is intended to eject foreign substances from the tracheo bronchial tract The diaphragm, according to Coryllos, plays its role in inspiration only, most of the expiratory force is supplied by the abdominal muscles In pathologic states involving the bronchi it is well to recall that cough may act retrogressively and may drive foreign substances deeply into the alveoli

Expectoration

Mucus is elaborated by secretory glands lining the bronchial tree Its function appears to be the maintenance of a moist lining membrane and the entrapment of irritating foreign substances Its movement is facilitated by the presence along the bronchial mucosa of undulating cilia which have the capacity of propelling foreign material in the direction of the pharynx The movement is further enhanced by a modicum of peristaltic activity along the bronchiolar tree These activities, combined with cough, usually suffice to rid the lungs of foreign substances

Pulmonary Function Studies

Ventilatory equivalents The combination of ventilatory and respiratory functional figures into a single correlated expression has long been the aim of pulmonary physiologists This expression, known to many authors as the *ventilatory equivalent*, indicates the amount of ventilation required for the removal of a known amount of oxygen Cournand and Richards have pointed out that the normal male must ventilate between two and three liters of air in order to absorb 100 cc of oxygen A high ventilatory equivalent indicates that more air must be ventilated in

order to achieve sufficient oxygen absorption It places the site of hypofunction in the region of the alveolar membrane without differentiating between circulatory and diffusional deficiencies The ventilatory equivalent is increased in cardiovascular disease because of retarded circulation and oxygen utilization In a variety of parenchymal pulmonary diseases it is similarly increased where the alveolar membrane is a quantitative or qualitative barrier to oxygen diffusion Since ventilatory impairment may in many instances proceed apace with the respiratory deficiencies misleading figures may be obtained which may fail to reflect the true functional status Attention to collateral studies particularly the maximal and minute ventilation figures will assist in the proper interpretation of the ventilatory equivalent

Bronchospirometry Bronchospirometry has been introduced in an effort to study more precisely the competency of the separate lungs and their individual lobes In essence it consists of the introduction of double barreled tubes into the major bronchi and through the agency of inflatable cuffs which separate and seal off the two lungs from each other allow the quantitative and qualitative study of their individual gaseous contents The acceptance of bronchospirometric results without proper consideration for the many variables that are introduced has been criticized by many workers It has been pointed out that patients are under considerable stress have had topical anaesthetization breathe through a narrow tube and exhibit a wide variety of pulmonary vasomotor and secretory reflexes through the introduction of an irritating foreign body Furthermore these reflexes may be evoked unevenly because pathological conditions particularly of the bronchi are unequal on the two sides Under certain circumstances as in paradoxical respiration arising from a flaccid chest wall flow of air across the carina from one lung to the other has been postulated The relative importance of this phenomenon cannot be estimated by bronchospirometric methods since the interposition of a mechanical barrier between the two sides renders it inoperative

Probably the most serious bar to acceptance of bronchospirometric results is the fact that they are obtained under conditions of rest rather than stress Reserve function therefore cannot be properly evaluated until a display of the lung s capabilities is evoked This display is further prevented by the use of pure oxygen in the usual bronchospirometric determinations It is virtually impossible to produce oxygen debt under such circumstances It is also impossible to measure oxygen diffusion

through the alveolar membrane when the high gradient, produced by the presence of pure oxygen, cancels out retardation at the membrane Studies are currently being conducted by Ornstein, Meyers and Diamond wherein the latter objections are overcome by combining bronchospirometric techniques with the room air rebreathing bag tests which will be discussed under "newer pulmonary function studies," *v infra* These workers feel that an accurate estimate of the degree and character of individual lung impairment may be made through the use of this newer method

Newer pulmonary function studies We may now turn to some of the newer pulmonary function studies which are being performed in an effort to more clearly understand the state of the pulmonary tissue It has been pointed out that disturbances in lung function are usually ventilatory or respiratory or combinations of these two It has also been indicated that cardio circulatory dysfunction may simulate purely pulmonary dysfunction and must be carefully differentiated Frequently this is made difficult or impossible because of the inter relation of clinical manifestations This is well illustrated in post operative acapnia where excessive elimination of carbon dioxide, through deadening of the vasomotor center, produces peripheral loss of vascular tone, hemic stagnation and shock This progresses to pulmonary oedema, further impediment to gaseous exchange and a more profound degree of acapnia It is difficult to properly assess the role of each system in states of this character Resort to careful history, fluoroscopy, electrocardiograms, circulation times and venous pressures at times will render assistance Often they are of no value

The inter-relation and mutual interdependence of all of the above factors stimulated the search for a simple test which would assimilate all of them at one time The increasing recourse to resectional surgery highlighted the need for such a test It was reasoned that since the goal of respiration was the transport of atmospheric oxygen to the tissues, any test which would measure its rate or degree of removal from a given reservoir would at one time indicate the competency of the transport system For this reason Ornstein, *et al*, devised a rebreathing bag of one liter capacity with a mouthpiece which allowed rebreathing of its atmospheric air for a period of twenty seconds after a standard exercise procedure * The residual air was then subjected to differential analysis

*For bedridden patients a modified exercise, utilizing arm activity is substituted for the eight inch 30 times "step up"

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Oxygen utilization and carbon dioxide excretion were thereby measured and normal values ascertained For convenience, the normals were established on the basis of residual volume rather than utilized volume Results were gratifyingly consistent and many hundreds of subsequent determinations have added experience in their interpretation Beginning with atmospheric oxygen in the rebreathing bag, the normal male will leave 7 95 ± 0 851 volumes per cent after standard exercise The normal female will leave 8 30 ± 0 714 Normal males will increase atmospheric carbon dioxide of 0 03 volumes per cent to 8 09 ± 0 436 Females will increase it to 7 70 ± 0 497 Arbitrary limitations of normal values were obtained through experience, oxygen residuum within the rebreathing bag up to 10 volumes per cent is indicative of good pulmonary function Values above 10 indicate impairment The precise place of the carbon dioxide determinations has not as yet been established

The oxygen utilization study is combined with an estimation of the resting minute ventilation and the maximal minute ventilation From these the ventilatory factor is determined On the basis of these, a good estimate of the advisability of thoracic surgery can be obtained The fallacy of attempting to estimate lung function on the x ray appearance has repeatedly been demonstrated The crippling attributes of thickened pleura, the scattered albeit minor lesion the fixed diaphragm the emphysematous state have been emphasized It has been shown that extensive lesions may be associated with highly useful lung tissue which allows major surgery which was seemingly excluded by x ray survey alone Post operative determinations approximate those made pre operatively This is not surprising since diseased lung tissue, whether compressed or resected contributes little to ventilation or oxygen utilization Occasionally this oxygen utilization may even be improved post operatively This is interpreted as indicating the elimination of blood pollution resulting from circulation through a diseased area All or most of the blood traversing the lesser circulation does so through areas in which proper gaseous exchange can occur Post operatively we have rather uniformly noticed some diminution in ventilatory capacity as manifested in the maximal minute ventilation This is probably more the result of fixation of the hemithorax than of elimination of functioning lung tissue Late post operative function studies are currently in progress but no statement can be made at this time Preliminary estimates suggest that through exercise and muscular training near pre operative values for ventilation may be anticipated

These function studies have shown their special usefulness in the estimation of the operability of the doubtful or borderline cases Through them we have developed the courage to allow total pneumonectomy in the presence of contralateral pneumothorax, nor have post-operative pulmonary cripples been seen It is certain that this would not have been attempted without evidence that despite the presence of a destroyed lung and a contralateral pneumothorax, pulmonary function was adequate

Pathologic Physiology

A wide variety of pathologic states may impair the competency of physiologic respirations Their manifestations are many and frequently of multiple origin It is often impossible to distinguish circulatory, metabolic or cardiac disturbances from those of pulmonary origin since each may manifest itself as a respiratory symptom complex A few of the important ones follow

Anoxia This condition is more accurately termed "hypoxia" for obvious reasons It indicates unavailability of oxygen for tissue metabolism The origin of this state may be found anywhere along the line of oxygen transport from atmosphere to cell and may include the atmosphere itself in instances where its tension may be inadequate for proper delivery to an otherwise intact system The presence of inert gases instead of oxygen may produce the same situation Obstruction within the major air passages may result in hypoxia Blockage at the alveolar membrane not infrequently produces this state, the defect may be one of ventilation or diffusion It may combine both Inflammatory pulmonary exudate, oedema, emphysema and pneumothorax are examples Cardiac and arterio-venous shunts, by by passing the alveolar membrane, cause pollution of the circulation and a relative tissue anoxia Anemia reduces the vehicle of transport, hemoglobin, carbon monoxide and other chemicals render hemoglobin incapable of functioning for oxygen transportation Failure of maintenance of the circulatory rate, seen most commonly in shock and cardiac decompensation, reduces the rate of oxygen delivery Finally, delivery may be interfered with at the tissue level by any substance which interferes with the enzyme-oxidase complex Most authors point out that various combinations of the above mechanisms are possible

The diagnosis of hypoxia is not always easy This is partially due to cerebral effects which commonly overcloud the clinical picture The

patient is often euphoric and apparently cooperative He is usually restless In a more profound stage of hypoxia he is manifestly disoriented or deeply depressed Cyanosis only occurs under conditions which will be outlined below

Dyspnoea Dyspnoea or "difficult breathing" has been variously described but in general may be considered as the subjective consciousness of the need for increased ventilation Although usually having its origin in the hypoxic state, dyspnoea is essentially a ventilatory phenomenon It also occurs in acidosis cerebral injury and emotional upset In lobar pneumonia and possibly in pulmonary oedema, dyspnoea is thought to originate from increased sensitivity of the Hering Breuer reflex

Cyanosis Cyanosis is that bluish discoloration of the skin and mucous membranes caused by the presence of five or more grams of reduced hemoglobin per hundred cc of blood It has various origins In polycythemia, extremely high hemoglobin concentrations make possible the mobilization of five grams of reduced hemoglobin with the slightest reduction in capillary circulatory rate This rate reduction produces cyanosis in normal individuals but must be of greater degree, in anemic states which approach five grams of hemoglobin, cyanosis is not seen since the required amount of reduced hemoglobin cannot be attained Cyanosis is most dramatically seen in cardiac or arterio-venous shunts It varies in intensity in pulmonary infiltrations, asthma or other conditions which interfere with oxygen delivery In each instance the blood is denied the opportunity of exposure to adequate alveolar oxygen concentrations Of interest is the occasional relief of cyanosis in pulmonary conditions through collapse of the affected area The explanation is simply a matter of shifted circulation and blood volume Pollution has been eliminated

Acapnia Acapnia is the term which denotes diminished blood carbon dioxide This is of special interest in the post operative period and particularly after thoracic surgical procedures Its origin is usually shallow breathing or tachypnoea without hyperpnoea This, in turn, stems from reduced circulatory rate or acute blood loss, each of which produce anoxia without carbon dioxide increase The vasomotor center is quickly affected by this diminished carbon dioxide supply and, in consequence, vascular tone is reduced Pulmonary stagnation and congestion follow

Tachypnoea will also produce the "Bohr effect" if unchecked This is due to excessive loss of carbon dioxide, which is necessary at the tissue level for the proper dissociation of oxyhemoglobin In its absence, oxygen

is not liberated but is retained at lower tension At the alveolar level, carbon dioxide is further lost because of its rapid diffusibility The effect, therefore, is twofold, insufficient carbon dioxide is available to stimulate the respiratory center and break the pattern of tachypnoea while, on the other hand, oxygen is not made available for adequate maintenance of tissue metabolism This combination of events may so depress the vital centers as to ultimately render them insensitive to proper stimulation That the therapy of acapnia is the liberal use of carbon dioxide is self evident

Gas absorption The mechanism of gas absorption from a closed space has long been the subject of dispute In 1930, Coryllos and Birnbaum, on the basis of animal experimentation advanced the theory which has received the widest acceptance It is perhaps best expressed in the description of air absorption from a blocked alveolus The essential feature is the disparity between the concentrations of oxygen and carbon dioxide in alveoli and venous blood and the interplay of nitrogen in the maintenance of atmospheric pressures Oxygen, having greater concentration in the alveolus than in the venous blood, seeks equilibrium by diffusing into the blood Carbon dioxide, for the same reason, diffuses into the alveolus Nitrogen, being equal on both sides of the membrane, has no impulse to diffuse But the pressure gradient for oxygen is considerably steeper than that for carbon dioxide, whereupon a considerably greater volume of oxygen is lost to the alveolus than is gained in carbon dioxide Since total reduction in volume means reduction in pressure, atmospheric pressure, transmitted through the soft tissues of the chest, is brought to bear in order to reestablish the proper alveolar pressure This per force increases the partial pressures of nitrogen and carbon dioxide which are impelled to propagate the diffusion process In so doing, they elevate the partial pressure of oxygen and passage of this gas into the venous blood is stimulated *A cycle is thus established which concludes with total collapse of the alveolus*

Authors who accept this mechanism usually state that it is the fundamental mechanism for gas absorption from any closed space They feel that it is equally operative in the pleura, the peritoneum, the blocked pulmonary segment, lobe or lung It is felt to be the basic factor in the production of atelectasis, the closure of pulmonary cavities, the removal of subcutaneous emphysema, the elimination of air following perirenal insufflations and air encephalography

Ornstein *et al* were unable to confirm this hypothesis for pleural air

in an exhaustive study of the behavior of pleural gases They found that in 145 observations of the gaseous contents of the pleural spaces of patients with artificial pneumothorax the equilibrium concentrations of oxygen were invariably lower in the pleural space than in the capillary venous system and that the concentrations of carbon dioxide in the pleural space were higher These consistent observations controvert the commonly given explanation of gas absorption for pleural spaces since the gases involved are obviously not seeking equilibrium between pleural space and venous blood In a study of bilateral pneumothoraces Herman Ornstein and Friedman showed that gas absorptions from the two sides were dissociated and independent phenomena Were the gases in equilibrium with the capillary venous circulation they might have been expected to have been roughly equivalent This was not the case These workers concluded that carbon dioxide and oxygen reflect the metabolic processes of the pleural tissues and take part in oxidativ mechanisms Oxygen is thereby utilized carbon dioxide eliminatec They feel that gas absorption is essentially a function of the nitroge This inert gas might be expected to retain equilibrium with the tissu and the venous system actually the pressure and volume of nitrog was always higher in the pleural space than in the tissues and capillar This is probably due to the pressure of the expanding lung and pressure of the atmosphere operating through the soft tissues Whatever the cause the constantly elevated pressure impels diffusion from the pleural space into the capillary system

It is essential to note that the concentration of gases in the pleural space varies under abnormal conditions It has often been shown that in the presence of effusions and particularly in empyemata unusually high concentrations of carbon dioxide and low concentrations of oxygen are found The explanation is obscure under the Coryllos gas reabsorption theory but is readily elucidated by the theory proposed by Ornstein *et al* which is premised on the heightened metabolic activity of infected tissues

Alteration of gas concentrations in the pleural space is commonly observed in the presence of bronchopleural fistulae Here we are no longer dealing with a closed space since mixed atmospheric and alveolar air is introduced into the pleural space causing profound dilution Abnormally high concentrations of oxygen and low concentrations of carbon dioxide in samples taken from the pleural space should lead one to suspect the presence of bronchopleural fistula It should also be noted

that fistulae may be intermittent as will be demonstrated from serial gas analyses

Cavity closure We are in full agreement with Coryllos' and Eloesser's opinion that closure of pulmonary cavities depends on closure of their draining bronchi An extended discussion of this mechanism would more reasonably appear in a discussion of pathology Suffice it to say that this belief stems from innumerable clinical observations and a tremendous post mortem series wherein the correlation between open cavity, open bronchus, and closed cavity, closed bronchus has been invariable Following bronchial closure there is reabsorption of gases until cavity closure is accomplished The precise method of reabsorption is not clear and probably varies in every instance in accordance with the variable nature of the internal aspect of the cavity wall Most important are the vascular and fibrosis factors What is the state of the zone of vascular granulation tissue? How heavily is it covered with caseation? Serial gas analyses of a cavity with a blocked bronchus will settle many of the residual problems

Oxygen lavage This therapeutic measure was introduced by Welkind and Herman to accelerate the reexpansion of lungs collapsed by pneumothorax It consists of the introduction of two needles into the pleural space and the passage through one of them of a constant stream of oxygen The other is connected to the deflation side of a pneumothorax apparatus and serves to maintain reasonable pressures The mixed pleural air is thereby largely replaced with oxygen Extremely rapid lung reexpansion is obtained with this method Gas analyses at various phases in the process indicate rapid return of the differential gas concentrations to the levels noted above It seems logical to assume that both oxygen utilization in the metabolic activity of the pleural membrane and diffusion through the pleura into the capillary system occur during the phases of high oxygen concentration In the later stages only the former operates Similarly, in the initial phase the return of carbon dioxide and nitrogen into the pleural space is stimulated by the steep pressure gradient The oxygen withdrawal apparently occurs at a considerably greater rate than its replacement since profound negative pressures are created by this method

In our experience oxygen lavage of the pleural space evokes lung re expansion at a faster rate than any other method This has application in those instances in which this accelerated rate is desired, such as in the presence of fibrin-containing effusions, the deposition and organi-

zation of which may threaten to encompass the lung in an unyielding envelope Re expansion may be accomplished before this limitation occurs In other instances it might be important to institute undelayed contralateral collapse, lavage minimizes delay

Pneumothorax The lungs are normally covered in all aspects by a thin membranous envelope which is reflected from the lung hilus to the inner aspect of the thorax This envelope is the pleura Its median reflections represent the lateral boundaries of the mediastinum The pleura has several functions It serves to keep the lung airtight and the hemithoraces separate It provides a sliding surface for the excursions of the lung in respiration and thereby allows greater expansion than could be anticipated were the lung frozen within the thoracic cage It was stated, *v supra*, that the apical posterior and the upper mediastinal posterior areas depend entirely upon root descent and pleural slide for their expansibility Another, and less well understood function of the pleura, is related to its capacity for sensitization It is probable that this function is fundamentally protective and reduces the incidence of pleural infection

The pleural space is normally only a potential space and bears a negative pressure of about seven centimeters of water This pressure is an expression of the elastic recoil of both lungs mediated through a non rigid mediastinum In pneumothorax therapy the lung is not ordinarily compressed but is usually allowed to contract because of its own internal elasticity The air that is introduced into the pleural space is usually *allowed* to flow in through suction it is not customarily "pushed" in

The initial artificial pneumothorax has been the subject of considerable discussion and a large literature Most workers are convinced that no excess of care or of ingenuity in the construction of special initial needles will allow manometric readings from a potential pleural space We agree with those who say that every initial pneumothorax is a traumatic pneumothorax and that a portion of the pleural air which is present after induction has been obtained from the lung This was first described by Tchertkoff and later more extensively studied and proven by Tchertkoff, Selikoff and Robitzek Final proof was provided by Herman, Ornstein and Friedman in their study of pleural space volumes which were invariably greater than the amount of air introduced These volumes are highly variable and depend upon the size

and number of lung punctures, the presence of underlying emphysema or blebs and the capacity of the lung to seal off spontaneously

Because of this phenomenon of trauma, pleural pressure readings are difficult to interpret in early induction phases When stabilization occurs, however, some measure of the conditions obtaining can be derived from careful study of these pressure relationships These pressures are a composite of the effects of an expanding thorax and an underlying lung which provides varying degrees of resistance to this expansion Thus, on inspiration, pleural pressures achieve greater *negativity than they do on expiration, a simple reflection of the* gas laws, the inverse relationship between volume and pressure of gas in a closed space under static temperature conditions

The negative pressure results from 1) outward pull of the homolateral thorax, 2) recoil of the homolateral lung, and 3) traction of the flexible mediastinum toward the contralateral side through the recoil of the contralateral lung As the collapsing lung becomes reduced in volume beyond its point of complete relaxation and as the mediastinum begins to exert an influence by resisting further movement into the contralateral hemithorax, the pressures assume less negativity Increasing resistance is now encountered in the form of a lung which resists efforts at compression beyond the point of elastic recoil, and a mediastinum which offers a *firm barrier to further shift This is reflected first* in diminished negativity of the pleural readings and eventually in true positivity which indicates that atmospheric pressures have been exceeded

The amplitude of the manometric fluctuations similarly has relevancy to the state of the underlying lung In general, it may be stated that a wide range of fluctuation indicates a lung which is not 'following' the outward thrust of the thorax The space is thereby larger, the pressure lower Since the underlying lung must fill with air in order to expand, the implication from the wide fluctuations would be that something hinders the lung from filling Such conditions are met with in atelectasis, pulmonary fibrosis, alveolus filling processes, inelastic and resistant pleural envelopments and strategically effective pleuropulmonary adhesions A diminished amplitude of fluctuation may indicate an underlying lung which is actively following the moving thorax or may indicate fixation of the thorax as a result of trauma, operation or systemic disease The factor which is responsible is usually

readily apparent Amplitude bears no relation to the degree of pul monary collapse

Positive pressures after relatively small refills or pressures which rapidly proceed from high negativity to considerably less negativity following refills indicate some fixation in the volume capacity of the pleural space and bespeak the presence of adherances which limit collapse These adherances usually appear in the diseased areas and commonly obviate selective collapse Occasionally, and particularly when they arise from a previous pleural effusion, they may not interfere with proper collapse

The question of high *vs* low pressures in the maintenance of thera peutic pneumothorax is one which is calculated to stimulate acrimony among the members of any group of phthisiologists Probably a middle position is correct Reverting to the gas laws, high pressures indicate a lung which is resisting collapse Since the aim of therapeutic pneumothorax is collapse and since high positive pressures indicate that this is not being obtained, nothing is gained by utilizing still higher positive pressure ranges Pinner points out that positive pressures in both phases of respiration abolish ventilation of the collapsed lung This must be true when the lung is freely encompassed by air It is not so in many of the anatomically bizarre yet highly selective and therapeutically effective collapses that are obtained

In evaluating pleural pressures it is important to use needles of proper size It is self evident that a needle of small gauge introduces more lag into the manometric recording of intrapleural pressures throughout the respiratory cycle than will one of large gauge In conse quence the amplitude of fluctuation is reduced and the extremes o fluctuation will not be realized This begins to assume significance wit needles of 23 gauge or less On the other hand, 19 gauge and larg needles are unnecessarily traumatizing and this larger size contribu nothing Insofar as initial pneumothorax is concerned, the auth advocate the use of the smaller gauges, even to the impairment of accuracy of the determinations, in order to minimize trauma to underlying lung which must inevitably occur Small needle techniq in which the lung is deliberately punctured in the induction of initial pneumothorax, have been described by Selikoff, Tchertkoff and Robitzek In this method the degree of trauma and of collapse are con trolled and minimized

The mechanism of *selective collapse* of the lung in tuberculosis has

been the subject of many explanations. A combination of mechanisms probably obtains. Initially atelectasis is of major importance. The atelectasis may be of lobule, segment, lobe or even of lung and may be isolated or scattered. It is produced by obstructing the air passage leading to the collapsed area and may be due to exudate, oedema, vessel engorgement or the presence of necrotic material. Later it may be due to organization. Whatever the immediate reason, air cannot enter the obstructed zone and the lung cannot follow the outthrust of the thorax as it should. Further shrinkage follows complete air absorption. Concomitantly, the factor of lost elasticity plays its role. It is to be recalled that the normal lung has resiliency or bidirectional elasticity. Normal lung parenchyma collapses and re-expands symmetrically under pneumothorax because the elastic fibers of the interalveolar septa and of the blood vessels exhibit their forces evenly in all directions. Tuberculous infiltrations, excepting caseation with liquifaction, do not destroy elastic fibers but so thoroughly disrupt their efficiency that much resiliency is lost. Which of these factors is of greater significance in any individual case depends upon the character and extent of the disease process and may not be easily evaluated.

Re-expansion of previously collapsed lung proceeds in accordance with well established principles. It must not have become so adherent as to prevent resumption of its original position. It must have retained its ability to slide smoothly within the pleural envelope. It must not be hindered in its expansive excursions because of restrictiveness of that envelope. It must not contain atelectatic foci, nor must it be fibrotic. The presence of any of these makes impossible complete restoration of ventilatory integrity. A lung collapsed for control of a tuberculous lesion obviously can never be free of all handicaps. In consequence, uneven and incomplete re-expansion is to be anticipated after all therapeutic pneumothoraces. Mediastinal shift and contralateral lung hypertrophy often provide some degree of compensation. The typical post pneumothorax hemithorax is variably contracted, contains a lung of diminished volume, has an elevated diaphragm and displays a homolateral mediastinal shift.

The rate of lung re-expansion, like its degree, is dependent upon certain factors, namely, the pleura, the state of the circulation and the internal condition of the lung. The role of the pleura is most important. When it is thick and fibrotic, nitrogen diffuses slowly and oxygen is metabolized at a reduced rate. This thickening, furthermore, offers

increased resistance to expansion requiring a greater negative pressure to overcome this resistance. This prolongs the rate of re-expansion. Under conditions of collapse a smaller pleural surface area is exposed to the pleural gases than is exposed under a condition of full expansion. That this increases the rate of re-expansion is self evident. A diminished circulation in the sub-pleural zone, especially when coupled with thickening of the pleura, interposes another retarding factor in gas reabsorption. If there is temporary atelectasis of the underlying lung, re-expansion may be retarded or even halted. The rate at which this obstruction can be overcome governs the rate of re-expansion in large measure.

Vital capacity is surprisingly unaffected by the induction of pneumothorax. This is probably due to the fact that lung constriction expresses residual air which is a fraction of total but *not* of vital capacity. It is also due to the fact that selective collapse of a diseased area compresses tissue which has already suffered reduction in its ventilatory functions. Compensatory contralateral hypertrophy has often been postulated. Obviously under pneumothorax the level of the midcapacity is lower. The only important alteration of ventilatory function which is seen with any regularity is a variable reduction in the maximal minute ventilation. The resting minute ventilation is not significantly changed. The ventilatory factor tends to be reduced. The implication here is that ventilatory changes are only appreciable under stress, another way of saying that the reserve has been reduced. Changes in oxygen utilization are discussed under "pulmonary function tests." Suffice it to say here that this phase of pulmonary function also shows remarkably little change. This appears to be due to compensatory contralateral improvements in efficiency.

All of the above phenomena relate to the closed pneumothorax space. No discussion would be complete without some mention of the *broncho-pleural fistula* which profoundly alters the problem. Bronchopleural fistulae may be acute or chronic. Acute fistulae which close, probably occur much more commonly than is generally supposed since evidence of their unsuspected presence is frequently seen at post mortem examination. They vary in size, position and character and therefore in their clinical manifestations. The smaller fistulae are often difficult to diagnose although they may be suspected from the presence of pleural pressures which are not as negative as expected by the presence of recurrent effusions and by systemic reactions.

Matsuzawa, who made important contributions in this regard,

showed that in these instances it is often necessary to perform gas analyses of the pleural gases Influx of mixed atmospheric and alveolar air introduces oxygen of 15 volumes per cent concentration for dilution with pleural gases Thus oxygen is elevated from its usual fractional level to five or more per cent Conversely, carbon dioxide may be diluted to fractional levels These figures may vary considerably from day to day, an observation which should suggest intermittency of the fistula

A wide open fistula gives gas analysis readings approximating atmospheric conditions These, however, rarely require gas analysis for diagnosis since other, simpler methods usually suffice Among these methods are (1) Observation of the pressure within the pleural space Wide open fistulae evoke constant readings above and below zero on expiration and inspiration (2) Following aspiration of air to negative pressures (if possible), the wide-open fistula quickly restores the pressures to their previous level (3) Instillation of a suitable dye substance into the pleural space is soon followed by its expectoration The most easily diagnosed fistula is probably the tension fistula which introduces a ball valve in the region of the cavity, its draining bronchus or the fistulous opening through the pleura The physical signs are those of tension and the pleural pressures are highly positive The x ray is often characteristic showing contralateral mediastinal shift, pulmonary compression and often atelectasis and a basal effusion

Pleural pressures here may be sufficiently high as to demand emergency action This has occasionally taken the form of pneumonectomy in suitable cases As a temporary expedient, a wide bore needle connected through a rubber tube to a water trap, will take off the excess pressure The greatest dangers with bronchopleural fistula are the development of empyema, particularly of the mixed infection variety, and aspiration of infected material into the contralateral lung

Thoracoplasty The current interest in resectional surgery has relegated the procedure of primary thoracoplasty to a distinctly secondary position in the surgical treatment of pulmonary tuberculosis It is still widely used as an adjunctive procedure following pneumonectomy in an effort to reduce dead space, prevent cardiac displacement and diminish distension of the contralateral lung Whether these ends are served by this procedure, or whether it is essential that efforts should be made to serve them are questions that will be resolved when long term follow up studies have been completed The question of lung distension will be discussed under ' emphysema

The procedure of primary thoracoplasty has been standardized in large measure and consists essentially in the removal of ribs or rib segments over the area of disease The procedure is customarily performed from above downwards and most surgeons make every effort to remove the longest segments possible This means removal of the rib, variable lengths of cartilage and often the transverse processes This may be supplemented by mobilization of the lung apices in the extrapleural plane The result is a non rigid chest wall which no longer supports expansion on inspiration Indeed, the immediate post-operative period in instances wherein the rib removal has been extensive, is often characterized by a paradoxical retraction of the area involved during the inspiratory phase

This plastic chest wall allows the underlying lung to relax and contract in essentially the same manner as when air is introduced into the pleural space The lung utilizes its inherent contractility Minor compressive force is supplied by the combined weight of overlying soft tissue and exudate, the latter being derived from traumatized extra pulmonary tissues This compressive force is of minor significance and becomes progressively less important as the exudate reabsorbs and the chest wall stiffens The major factor determining the degree of collapse, assuming adequate rib removal, is the state of the underlying lung The principles governing selective collapse in pneumothorax are again operative so that the degree and character of collapse depends upon an interplay of the forces of recoil or retractive elasticity, resistive elasticity or the tendency of the lung to retain its shape when compressed, the absolute amount of tissue loss through necrosis, stiffening of the lung through fibrosis and finally, atelectasis, the degree depending upon the fate of the bronchial tree These factors explain the satisfactory results often resulting from seemingly poor anatomical collapse and conversely, the failures despite seemingly excellent collapse Review of the pre operative x ray films will not infrequently indicate what type of anatomical result might have been anticipated from consideration of the above factors

The reduction in pulmonary ventilation following thoracoplasty is highly variable and depends upon a number of factors The extent of the thoracoplasty is most important, but the factor of ankylosis and fixation following bone regeneration plays a not inconsequential role since fixation of the thorax nullifies the usefulness of normal lung tissues

encased in a non expanding thorax The factor of greatest importance in the retention of ventilatory capacity is the maintenance of a functioning diaphragm It has repeatedly been our observation that the approximate degree of ventilatory loss can be predicted from preoperative fluoroscopic observations of diaphragmatic mobility

It has been uniformly observed that the ventilatory effects of thoracoplasty are seen most in the reduction of the maximal minute ventilation The resting ventilation is but little altered, but under conditions of stress there is a noticeable defect in maximal ventilation In general, the changes in ventilation are not unlike those recorded under collapse by pneumothorax

The effects of thoracoplastic collapse upon gas diffusion have not been sufficiently studied to warrant definitive conclusions It may be generally stated that utilization of oxygen is moderately reduced, largely due to diminished ventilation and exposure of air to respiratory epithelium, but the effect of compensation through improved function of the contralateral lung and homolateral lobe mitigates this reduction This question is discussed more fully in the consideration of gas exchange in bronchospirometry

Bronchial obstruction The absolute and relative increase in the incidence of carcinoma of the bronchus makes bronchial obstruction a topic of increasing significance The mechanisms involved are relatively simple and are essentially the same whether the obstruction originates from the internal aspect of the bronchus, the wall of the tube, or by compression from a source entirely external Foreign bodies, neoplasms inflammatory lesions, enlarged lymph nodes, pressure exerting aneurysms, all may manifest themselves by impeding the easy flow of air through the tube system These manifestations vary with the degree of blockage

Minor obstruction may first express itself by the production of a mild and transitory wheeze, this indicates minor disturbance to the smooth flow of air and through the induction of vibrations, expresses itself as an abnormal sound Due to the shortening and narrowing of the bronchus in expiration the wheeze is usually best heard in this phase The next stage of obstruction is best perceived fluoroscopically and the manifestations rest upon the fact that air traverses a stenotic area less rapidly than it does a normal bronchus Inspiration may be unrevealing On expiration however, air leaves the normal lung at its accustomed rate but is momentarily delayed behind the block This causes a relative

increase in the illumination on the affected side It also is responsible for relatively greater pressure behind the point of blockage producing a shift of the mediastinum to the side of relatively lower pressure and delaying the expiratory diaphragmatic elevation on the homolateral side *Increasing blockage shifts the emphasis from the expiratory to the* inspiratory phase of respiration Air, being denied ready entrance to the involved lobe or lung easily enters the normal side and establishes relative pressure differentials between the two sides The mediastinum thereby shifts to the homolateral side on inspiration and the illumination is better on the uninvolved side In many instances, the expanding thorax, unaccommodated by air influx through the point of obstruction will induce sufficient negative pressure to produce paradoxical elevation of the diaphragm leaf on the affected side (Kienbock's phenomenon)

Careful observation and study may be required to establish whether the paradoxical movement is the result of this mechanism or of an involvement of the phrenic nerve since the differential diagnosis may rest on this point With complete two way blockage, there is rapid reabsorption of air and production of total atelectasis in the area obstructed This proceeds in accordance with the theory of gas absorption described by Coryllos and discussed above When sufficient lung tissue has been collapsed, there is retraction of the mediastinum, diaphragm leaf and thoracic cage. A rather large fraction of the lung volume must collapse to induce these retractions due to the propensity of the residual lung tissue to compensate by overaeration This is especially true in children

Of interest and of significance yet to be determined is the "atomizer effect' produced by tight bronchial stenosis It is of theoretical import ance in pulmonary tuberculosis and has been widely discussed although we have not seen conclusive proof of the existence of this mechanism Supposedly, on expiration, liquified secretions are forcibly ejected through a stenotic bronchus inducing the production of small droplets This occurs through the phase of expiration and perhaps beyond it since the blocked lobe or lung evacuates itself more slowly than does the normal lung On inspiration the nebulized and potentially tubercle bacillus laden air is drawn into the contralateral lung, serving thereby, to ensure contralateral seeding Roentgenograms tend to support this hypothesis but we should like to see a practical demonstration through the bronchoscope

Emphysema The problem of emphysema has been revitalized

through the increasing emphasis upon resectional methods in the therapy of an increasingly wide variety of pulmonary conditions The profound mediastinal displacements and the compensatory hyperaeration of the contralateral lung that has been seen so commonly following excision without subsequent thoracoplasty have aroused considerable speculation concerning the possibilities of dysfunction due to (1) right heart failure (2) reactivation of tuberculous foci due to stretching and possible rupture of incompletely healed capsules and (3) the development of crippling emphysema These problems have been of considerable interest to us The first cannot be answered at this time since a sizable series of cases of this type have only recently undergone this type of surgery The second question is for the pathologist to answer It would appear that completeness of healing density of the capsule and the degree of over stretching are determinants The question of emphysema is also a long term study but current observations are significant

In advanced emphysema ventilation is seriously impaired Complemental air is reduced residual air is greatly increased The tidal air may be normal the vital capacity is invariably less than the calculated normal Resting minute ventilation is moderately reduced the maximal minute ventilation is most seriously impaired

The exchange of gases in well established emphysema is similarly impeded This is due to a combination of poor ventilation which prevents exposure of proper gaseous concentrations to respiratory epithelium alveolar deficiencies resulting from reduced surface areas thickened membranes and obliterated capillaries and retardation of the lesser circulation

Emphysema must be differentiated from simple hypertrophy and hyperaeration and this is most conclusively accomplished through a study of the ventilatory and respiratory functions

There is an interesting relationship between emphysema and induction of pneumothorax which deserves comment It has already been stated that we believe that all induced pneumothoraces are actually traumatic In a recent experimental study we were able to show that every instance of respiratory distress following induction of pneumothorax and every instance of unusually large space within the immediate post induction period (many of the latter patients admitted to no distress) occurred in the presence of impairment of function of the contralateral lung It is our belief that this contralateral impairment whether due to pleural effusions fibrosis pneumothorax or actelectasis

produced a compensatory hypertrophy of the homolateral lung, probably associated with blebs, conducive to the excessive escape of air on introduction of the pneumothorax needle In no single instance wherein the contralateral lung was normal did we encounter excessive respiratory distress following pneumothorax induction

Spontaneous idiopathic pneumothorax behaves essentially in the same manner as one induced artificially That it is not due to tuberculosis is now widely known The pathogenesis is apparently rupture of a sub pleural bleb or perforation of a weak spot in the pleura Probably every case has some element of ball-valve mechanism which contributes to a local pressure increase and rupture Following repair of the rupture, the pneumothorax behaves in a manner identical with the artificially induced pneumothorax

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CHAPTER II

INFLAMMATORY BRONCHIAL DISEASES AND BRONCHOLITHIASIS

BRONCHITIS AND BRONCHIOLITIS

By Edwin R Levine M D and William S Klein, M D

Introduction

THERE is perhaps no affliction of mankind more common than bronchitis No age period through life is entirely free of it nor is any race of man immune Like all ordinary things, it is considered as a natural occurrence and little attention is paid to it There is enough evidence, however, to indicate that even in its mild phases it is not an innocuous condition Today when real therapy is available, it is import ant to remember this and by active intervention prevent the compli cations and eliminate the long term chronic diseases

Definition

Bronchitis may be defined as a pathological entity with an inflam matory reaction in the bronchial tree Inflammation alone does not constitute the disease since all city dwellers and all smokers show bronchial inflammation to some degree and it would be incorrect to classify all these persons as cases of bronchitis The inflammatory reac tion must be sufficient to upset the normal physiological mechanism of the bronchi and to produce evidence of disturbance of one of the phases of respiration This is exhibited by the appearance of signs and symptoms of such disturbance as listed below

Classification

Bronchitis is generally classified as acute and chronic This implies that the disease exists as an acute manifestation with severe symptoms which is self limited or which may go into a chronic condition or exists in the latter form It is not completely correct to make such a statement The chronic or long term bronchial disease may be punctuated by episodes of acute manifestation These may be mistakenly considered

as evidence of bacterial invasion on acute basis when they represent in actuality an exacerbation of a well established and deep seated disease It is obvious, therefore, that since both treatment and physiological effects will be varied by the duration of the disease, it is important to consider the condition as a whole rather than a short or long term illness

Another approach is related to etiological factors Consequently bronchitis may be classified as allergic, infectious, or traumatic This would include chemical irritation, irritation due to dryness, foreign bodies, and extrinsic pressure It is also possible to consider bronchitis from the standpoint of pathological changes Consequently we would have catarrhal bronchitis, suppurative bronchitis, obliterating bronchitis ulcerative bronchitis, and infiltrating bronchitis with peribronchitis The term obstructive bronchitis, would not be of any value in classification since this mechanism might occur in any type of bronchitis

It may also be noted that bronchitis may occur as a generalized disturbance involving the entire bronchial tract, or it may be localized to some definite anatomical division

Etiology

INFECTION

This is the most common etiological factor in bronchitis In fact, it is customary to think of bronchitis as evidence of infection in the bronchial tree unless one of the other causative factors is very obviously present When we consider the very large volume of air that enters the trachea in the course of every day, it is obvious that if any organisms were present in this air only an excellent defense mechanism could prevent universal and constant infection

In the average person approximately 10 000 cc of air enters the trachea every minute 600 000 cc an hour or 14 400 000 cc every day Bacteria viruses and fungi are present at all times in the air the number being very much increased in congested places or during close contact with other individuals Furthermore, the mouth and throat are constantly occupied with the organisms known as 'the normal flora plus other temporary residents acquired on contact with infected individuals *If anyone ingested one gallon (4000 cc)* of water or any amount of food containing as many pathogenic organisms as does 'fresh air, more or less illness would be expected The aspiration of not one

but 3000 gallons of air daily without constant infection is a tribute to the excellent defense mechanism of the respiratory system

This mechanism consists of (1) cilia, (2) narrowing of the bronchus on expiration, (3) cough, and (4) a peristaltic action Consideration of these is important to the understanding of symptoms and also because treatment must be directed at restoring these functions to as nearly normal as possible

Ciliated epithelium exists as a lining of the trachea and bronchi The motion produces a constant wave upwards and outwards towards the glottis Almost any foreign material, except large foreign bodies, can be washed out in this manner Consequently, pathological changes which destroy the cilia or interfere with their action remove one of the finest defenses and predispose to recurrent infections

The fact that the bronchi are elongated and widened on inspiration and shortened and narrowed on expiration, is not only valuable as a means of diminishing dead space, but acts as a method of expelling undersirable materials This change in lumen causes a very marked increase in the rate of flow of air particularly during the early portion of expiration Consequently there is a tendency to blow out anything which may be in the bronchial lumen This factor is increased by cough which is the most potent of the defenses A cough clears the bronchi of offending material by a sharp blast rather than a steady flow of air

The most constant mechanism is a peristaltic action of the bronchial musculature which forces material upwards and outwards Although the anatomical structure of the bronchi makes it difficult to understand how the walls can be approximated, these waves can be seen easily by fluoroscopy using iodized oil

These are the four means of preventing infection from becoming established in the bronchi In addition, there are, of course, the biological defenses which make up the resistance of the body to infection If, however, any organisms are implanted, these mechanisms of defense may be stimulated to a type of activity that aids rather than inhibits the disease.

Considering the volume of air, the fact that it is always contaminated, and the mechanism of defense, it becomes apparent that the causation of bronchitis by infection is a result of diminution of these mechanisms It is not simply an invasion or an aspiration as is the cause in traumatic bronchitis Consequently, the organisms most commonly

associated as causative agents are the ones most commonly found in the pharynx These will vary with the season, and the type of infection present in the community

In addition to these, there are viruses which are difficult to identify and which may be associated with bacterial infection Virus infection generally is the initial one and in these cases the bacterial invasion is secondary and complicating

ALLERGY

The second main category of etiological factors is allergy Whether the allergen is directly implanted on the bronchial mucosa by inhalation or the reaction be part of a general constitutional process, the effect on the bronchi is very much the same

There are three types of changes which allergy causes in the bronchi The first is a contraction of the bronchial musculature, the second edema of the mucosa and third, production of a thick white mucous secretion These vary in degree from very slight changes in one or all types, to severe changes by all three mechanisms This latter condition results in true asthma It may be noted that since these allergic changes also lower or interfere with the normal defense mechanisms of the bronchi infection follows sooner or later and the etiology of the bronchitis is mixed

Whatever the mechanism of allergy involved, if the bronchi are infected, an allergic bronchitis soon occurs It may be argued that a simple allergic disturbance of the bronchi does not represent actual bronchitis This is true of allergic disturbances of short duration and that occur at infrequent intervals However, any such change which lasts for a period of time or recurs within short periods, invariably results in inflammatory changes In fact, if such a condition attains any degree of chronicity, bronchial infection occurs and the end result is always an infectious bronchitis The mechanism of this is associated with the double factors of loss of the normal defense against infection and partial bronchial obstruction causing the retention of secretion The former mechanism results in the presence of infection should an invading organism be present Once this has occurred, retention of secretions not only maintains the bacteria in contact with the bronchial mucosa, but maintains also, a constant irritation which is in itself the source of increased bronchial secretion Thus an allergic manifestation

which alters the bronchi on a temporary basis, without any permanent anatomical changes, may result in severe and permanent bronchial pathology

TRAUMA

The last of the major factors in the causation of bronchitis is trauma Although conditions change somewhat according to the traumatic agent, the resultant inflammation is different more in degree than in kind This term is used to include all irritating substances or conditions and includes the inhalation of chemical irritants such as chlorine, freezone, SO_2, etc These produce inflammatory changes in the bronchi and frequently a very diffuse bronchitis Physical irritants which include many industrial dusts as well as actual foreign bodies produce an irritation and inflammation of a foreign body reaction The degree of the reaction depends on the amount of irritation produced by the particular substance Sawdust for instance is not nearly as disturbing as is the dust of cotton or fur The reader is referred to sections on The Pneumoconioses, Bagasse Disease, and Pulmonary Diseases Caused by Noxious Gases, Fumes and Dusts

One of the most important physical irritants is mineral oil This was overlooked for a long time because its action is so slow that a causal relation was not established However, it has been established that even small amounts of this oil will remain in the bronchial tree and lung indefinitely and be a constant source of irritation Therefore the use of oily nose drops, oils, vaseline or oily ointments in the nose is an important factor in the production of a slowly developing but increasingly severe bronchitis Oil taken by mouth is not generally considered to be a cause of bronchial disturbance, but it has been shown that varying amounts may find their way into the bronchial tree and thus cause some irritation

Smoke, as such, and the multiple factors that make up the air pollution of some of our larger cities are serious causes of chronic bronchial irritation These are combined chemical and physical factors depending on the material in the air Not only does air pollution cause traumatic bronchitis of itself but even with subclinical irritation, there is the interference with defense mechanisms and the development of bronchitis on an infectious basis This explains the higher incidence of respiratory infection in areas where the air is laden with smoke and dust

Pathology

ACUTE BRONCHITIS

In acute bronchitis the changes are primarily in the mucous membrane which is seen to be red and swollen and may be dry or covered by secretion The epithelium is greatly congested and desquamates The submucosa is infiltrated with leucocytes and the mucous glands are distended In more severe cases, the bronchus is lined with mucopurulent or purulent secretion In the ordinary case, the inflammation subsides *without further complications and the mucous membrane returns to* a normal state However, it may become chronic or, as in the case of severe irritation involving the bronchioli, there may be complete obliteration of the lumen

CHRONIC BRONCHITIS

In the chronic stage, the mucous membrane may be swollen and hypertrophic, or it may be denuded or pale and atrophic The variation is due to the etiological factor and the duration of the disease Chronic infectious bronchitis frequently shows the hypertrophic mucosa while in allergic conditions the mucosa may be pale In very long standing cases, without severe infection, generally those associated with bronchiectasis or emphysema, atrophic mucosa may be found Microscopically, all the coats are infiltrated with leucocytes or round cells, or both Bronchitis and bronchiolitis of virus origin show round cell infiltration involving also the peribronchial tissue, and in the case of bronchioli further infiltration involving the interalveolar septa Late or long standing cases may show a replacement fibrosis which, in some cases, produces actual obstruction of the bronchioli This fibrosis, when involving the bronchioli, also involves the lung parenchyma causing serious interference with respiratory function

Physiology

The bronchial tree is essentially a conducting system composed of tubes of diminishing length and diameter finally becoming of microscopic size before terminating at the alveoli This is, however, not a static system, but a dynamic one During inspiration the bronchi elongate and dilate, while in the expiratory phase, the bronchi are shortened and narrowed The effect of this on respiration is to produce a larger amount of air in the chest during inspiration thus aiding by diffusion the maintenance of a high oxygen level in the alveoli The decrease in the volume of the bronchial tree during expiration diminishes the dead

space and thus increases the efficiency of respiration Another normal function is the constant action of the musculature and cilia to cause any foreign material lighting on the bronchial mucosa to be transported up toward the glottis and discharged Should the foreign matter be of greater size or be more irritating, the expulsive mechanism is cough

The mechanisms are varied considerably by inflammation and irritation of the bronchi In bronchitis there is an exaggeration of the narrowing of the lumen during expiration This is caused by the irritability of the bronchi and its over reaction to stimuli Consequently, there is a tendency for the lumen to become markedly narrow during expiration This is accentuated by forced expiration or by rapid breathing and may be demonstrated by the spirographic tracing, showing the difficulty of expiring air with forced or rapid respiration

It is noted that this difficulty in expiring air may not occur with quiet breathing and become apparent only during rapid respiration or an attempt to force air out rapidly Under such circumstances there is an entrapment of air within the chest This difficulty becomes increasingly severe in the presence of secretion, since when the lumen of the bronchus narrows, it may be filled partially or completely by the secretion, causing partial or complete obstruction The drainage of the bronchus is thus interfered with and produces a greater irritation and a more extensive infection Furthermore, the very force of attempted expiration produces pressure behind the obstruction and dilatation of the distal structures

If the infection is of long duration such as may occur in chronic bronchitis or subclinical bronchitis with frequent exacerbations, anatomical changes may result The retention of secretion sooner or later produces infection of the bronchioli, and this in turn, invasion of the interalveolar areas with resultant interstitial pneumonitis Although this latter development may be microscopic in extent and not visible on the x ray picture as fibrosis or infiltration, its effect on respiratory function is marked This is due to the slight change in the elasticity of the lung caused by this interstitial thickening and the consequent changes in ventilation Bronchitis therefore, produces changes in the physiology of the bronchi with interference of their normal function and as a corollary or sequel, interference in the function of the lung parenchyma

The expulsive mechanisms of the bronchi, as stated above, represents the most potent defense against foreign material of any sort in the respiratory system One of the earliest changes caused by inflammation

is the desquamation of lining cells and a loss of the ciliary action of the bronchial mucosa With the thickening of the membrane that occurs at this time, there is further loss of this mechanism of transferring of offending matter to the glottis without the necessity of cough Thus the patient with bronchitis is more susceptible to additional bronchial infections than is the normal individual What is perhaps more important, is that when a bronchus is already inflamed irritating substances remain on the mucosa longer and increase the irritation The last line of defense is then needed and is used to an extreme—the cough mechanism Cough is a response to irritating matter stimulating primarily, sensitive areas in the larynx, trachea and major bronchi

The stimulation of these areas produces a chain of events designed to get rid of the offending matter These were likened by Coryllos to the mechanics of firing a gun There is first a deep inspiration, corresponding to loading the gun Second, the glottis is closed and contraction of the muscles of the abdomen and the chest take place causing a positive pressure in the thorax like the pressure in the chamber when the powder is burned And third, the glottis is suddenly opened and the air of the trachea sharply expelled The diaphragm which has been depressed and fixed in the first two phases rises sharply in the last However, in ordinary coughing, it does not rise to its fullest height but seems to act as a controlling mechanism determining the amount of abdominal pressure that is exerted upon the chest This would appear to be related to the amount of irritation In mild irritation a single cough of no great intensity is sufficient If the irritation is more severe, the intensity of the cough is likewise increased and generally, there are several expulsive efforts for one inspiration with a closure of the glottis between each Here, the diaphragm can be seen under fluoroscope to rise a short distance with each effort When the irritation is very severe, as in the case of acute bronchitis, the cough becomes spasmodic in nature, a series of short, severe expulsive efforts followed by a quick, deep inspiration and again a series of coughs The picture is one of over reaction to a stimulus and so far from becoming a more efficient method of getting rid of irritating substances it defeats its own end by its very severity

As noted above, sharp respiratory efforts result in an increased narrowing of the bronchi In fact, if the effort is severe enough, the bronchi may remain contracted even during the sharp inspiration This spasmodic function results in a complete obliteration of the bronchial

lumen in the first few cough efforts The quick, sharp inspiration is accompanied by a crowing wheeze and little air enters into the lung The subsequent coughs, therefore, have less expulsive power since there is less air and the cough takes on the aspect of recurring spasms which accomplish little good, while they only increase the irritation

Since the cough reflex is stimulated only in the trachea and larger bronchi, it follows that involvment of the small bronchi alone and secretion in them will not produce cough Consequently, the presence of cough would indicate a collection of secretion in the trachea or major bronchi If secretion is distal to this, as frequently occurs in low grade chronic suppurative bronchitis, there is no cough until enough secretion is formed to reach these bronchi or unless a change of position causes the secretion to flow upward toward the major bronchi If such a patient should breathe sharply as in laughing, crying, or with exertional dyspnea, he may stir up this secretion causing it to reach the larger bronchi and produce spasms of cough following any of the above mentioned patterns

Symptoms

The most prominent symptom is cough There may be no other symptoms However, infectious bronchitis may show the symptoms of the infection, while the traumatic disease displays indications of irritation, and the allergic, the symptoms associated with that condition It is worth noting that in general these are the symptoms of the etiological factor and not primarily those of bronchitis, except as these are manifested through changes in bronchial physiology

Thus where infection is present or the bronchial lesion is part of a broncho pulmonary disease, the symptoms of infection are displayed in addition to those directly caused by the bronchitis Such symptoms may be malaise, fever, chills, pain in the chest, headache, soreness of throat, anorexia or weakness There may also be the symptoms of an acute or chronic infection of the paranasal sinuses, since sinusitis is a frequently associated disease

Traumatic or irritative bronchitis causes very severe coughing in most cases There may also be irritation of the mouth, throat, eyes, or nasal mucous membrane Wheezing and dyspnea may occur in severe or prolonged cases

Bronchitis of allergic etiology may act exactly as the infectious type. This may, however, be associated with rhinitis, urticaria, angioneurotic

edema or asthma Since infection supervenes if the disturbance lasts any period of time, the symptoms of infection may be present in both allergic and traumatic bronchitis The major symptom, however, is cough

Diagnosis

The diagnosis of acute bronchitis is made on a clinical picture of acute respiratory infection associated with cough Determination of the etiological factor is, of course, a more detailed problem Physical signs of wheezes or rhonchi are important but not essential It is however essential that an x ray of the chest be taken to eliminate a pneumonic process whether or not there are physical signs of this If a pneumonic process is found, it does not mean that there is no bronchitis, but simply that this latter process is part of a broncho-pulmonary disease instead of being limited to the bronchial tree History of exposure is important in the chemical or traumatic type of disease

Differential Diagnosis

Acute Bronchitis

The chief conditions which are important to differentiate from acute bronchitis are pulmonary tuberculosis, pneumonia, mycotic infections of the lung, foreign bodies and tumors Pulmonary tuberculosis and pneumonic infections of the lung can be eliminated by x ray and subsequent workup The diagnosis of the acute bronchitis should be made only in the presence of a normal chest x ray It should again be emphasized, that the difficulty of differentiating these conditions on symptoms alone is due to the fact that since the pathology is broncho pulmonary rather than pulmonary alone, the symptoms are largely bronchial and are therefore easily confused with bronchitis Mycotic diseases of the lung may also be differentiated by chest x ray and subsequent laboratory workup However, all mycotic diseases do not have a typical x ray and it is therefore desirable in refractory cases of bronchitis to make studies for fungi Foreign bodies or lung tumors represent a more serious hazard although an x ray picture of lobar or segmental atalectasis may be present if the bronchus is completely obstructed Partial obstruction may produce a negative x ray by ordinary examination While the cough and other symptoms may be indistinguishable from true bronchitis, the finding of a localized or one sided wheeze is always suspicious and should always indicate bronchoscopy This type of examination is generally a definite method of differentiating these conditions

CHRONIC BRONCHITIS

The diagnosis of chronic bronchitis can generally be made on a history of a long continuing cough invariably accompanied by a greater or lesser degree of expectoration Although certain other conditions will produce the same picture, they are bronchopulmonary in nature and productive of bronchial inflammation

There is nothing specific about the cough in chronic bronchitis It may be mild or severe It frequently occurs in recurring spasms and is most severe in the mornings after awakening and when the patient first goes to bed at night The physical findings will vary not only between individuals but in the same individual at different times Basal rales, wheezes or rhonchi may be found and when later examined, be entirely absent This is due to the low grade nature of the disease and the fact that the amount of secretion which is the cause of the adventitious sound is diminished Therefore, when secretion has been expectorated, a period will occur when the bronchi are relatively empty and thus physical signs will be absent

The conditions from which chronic bronchitis must be differentiated are tuberculosis, atypical pneumonia, bronchiectasis, bronchial tumors, and mycotic diseases of the lungs Since the one essential diagnostic procedure which can never be neglected in all respiratory conditions is an x ray of the chest, tuberculosis and pneumonia are rapidly eliminated by a positive picture Examination of the sputum for tubercle bacilli will be another method of determining the tuberculous etiology of symptoms The differentiating of bronchitis from bronchiectasis is frequently very difficult since chronic purulent bronchitis produces exactly the same clinical picture that is found in bronchiectasis Bronchography, with contrast medium, must be done in such cases to make a diagnosis Bronchial tumors, if long standing and therefore likely to be confused with chronic bronchitis, generally produce involvement of some area of the lung The x ray picture will cause suspicion of this and the subsequent workup is necessary to make the diagnosis However, if we are to wait for such evidence, we will allow patients to progress from operable to inoperable cases of bronchogenic carcinoma right under our eyes The findings that will cause suspicion of neoplasm, are as in the case of acute disease, a localized or one sided wheeze and a localized or one sided diminution in the intensity of breath sounds In addition, to this, it is well to state that any patient over the age of forty who has a chronic cough should have, in addition to chest x ray and

bacteriological examination of the sputum a cytological examination of the sputum, and if there is any cause of suspicion that is not a simple bronchitis the patient should be bronchoscoped It would not be amiss to say that every chronic cougher over the age of forty should have a bronchoscopy as a regular part of his examination Where such a procedure is possible, it is as valuable in this type of case as routine x ray or electrocardiography Under no circumstances should bronchoscopy be omitted if there are suggestive physical signs x ray shadows or even suspicious sputum findings The presence of a bronchogenic tumor associated with a chronic bronchitis is not at all unusual

Mycotic diseases of the lung generally give some pulmonary involvement and therefore are seen on the x ray film Cultures of the sputum for fungi, complement fixation and skin test are part of the diagnostic workup needed to eliminate these infections It was formerly thought that all mycotic infections were associated with profuse expectoration which had definite characteristics This is not necessarily true Many such infections have little if any expectoration whereas simple chronic suppurative bronchitis may be the cause of a considerable amount of thick or foamy secretion Detailed discussion of this subject is presented in the section on Pulmonary Mycoses

Course of the Disease

Acute bronchitis starts suddenly with the picture of an acute respiratory infection When the etiology is infection it may run a course ranging from 10 to 14 days with gradual elimination of symptoms and improvement in the clinical picture This has been considered the typical course of the acute bronchitis However investigation has shown that in a large number of individuals particularly those who are smokers or who are exposed to dust or polluted air, there is evidence of subacute and perhaps subclinical bronchial inflammation at all times In such individuals acute bronchitis runs a longer course and remains as a subacute condition unnoticed by the patient or doctor Its presence may be indicated by the recurrence of the clinical picture if the resistance of the patient is in any way lowered Consequently, in a fairly large number of people it must be considered that the acute is followed by a subacute condition which may remain for a long period of time

In extremely severe cases or in such circumstances where the resistance of the patient is poor the disease may extend to take on a pulmonary component with resultant lobular or bronchial pneumonia

In acute laryngo-tracheo-bronchitis edema of the glottis or trachea may occur interfering with the ventilation of the lungs

Acute allergic bronchitis may be of extremely short duration if not associated with infection On the other hand, if infection is present, or if the offending substance remains in the environment, this may become a chronic condition or go on to produce true bronchial asthma

TRAUMATIC BRONCHITIS

The course of the acute condition of this etiology depends very largely on the type of injury to the mucosa and the extent and the duration of the injury to the membrane For that reason the disease may be very transient in nature if caused by a few inhalations of irritating gas or dust It may however, in extreme cases, result in obliteration of the bronchial lumen and death of the patient from asphyxia In between these two extremes lie many different manifestations depending upon the substances involved It is well to remember that infection may, and generally does, enter into these cases as a secondary invader and frequently becomes a primary problem

CHRONIC BRONCHITIS

The course of chronic bronchitis is one of ups and downs, remissions and exacerbations Through most of its course it does not represent a sufficiently troublesome clinical entity to bother either the patient or the physician During this period which extends over years, progressive changes are occurring as was stated above The disease becomes clinically important only when one of two things occur

(1) There is an acute exacerbation or a new infection giving acute symptoms (2) Permanent irreparable changes take place making the patient dyspneic, weak, or causing him to cough in a troublesome manner In this latter category fall the gradual developments of bronchiectasis pulmonary fibrosis and emphysema This disease develops such permanency that it has been considered as a permanent pathological entity rather than a curable condition

Complications

The complications of bronchitis are due to the extension of the disease down the bronchi and the effect of this or of the bronchitis itself on the cardio-respiratory function Extension of infection down the bronchial tree leads to pneumonic conditions of one sort or another In such cases where the secretion is particularly thick, atelectasis results from bronchial obstruction Extension of the disease through the walls

of the bronchi produce peribronchitis and bronchiolitis causing involvement of the interstitial areas of the lung This may result in interstitial pneumonia if the infection is severe enough, or may simply cause a thickening and loss of elasticity of the whole lung unit This interferes with ventilation and also with gas exchange in the alveoli, and consequently, markedly reduces the efficiency of respiration At the same time as intersitial infiltration has taken place, partial obstruction of the bronchial lumen produces an increased pressure on the alveoli Since these have lost their elasticity, as mentioned above, the result is an over distention with ruptured alveolar walls, and the permanent changes of emphysema The sequel to all these changes is right heart strain and eventual cor pulmonale

Treatment

Treatment is divided into relief of cough, attack on the infection relief of wheezing and dyspnea and establishment of adequate drainage Since cough is the most prominent symptom of all bronchitis it is the one that must be first treated However, the treatment of cough does not mean its immediate abolition, which in most cases is an undesirable result This is because the abolition of cough abolishes the protective mechanism which it represents, and may result in the retention of secretions and the spread of infection Consequently, most therapy of cough is directed at the relief of spasm and at some diminution of the intensity and frequency of the cough

It is well to remember that since cough is a physiological mechanism it must be treated by understanding what has set this mechanism in motion, and just what is happening Consequently, there is no such thing as a uniform treatment to be used for all coughs The therapy rather should be varied according to the situation

Simple cough without spasm or wheezing or any of the other manifestations, to be discused later is the sort of thing generally described by the patient as "just cough' This is usually associated with a tickling sensation in the throat, and may or may not be associated with the expectoration of sputum It is seen in acute bronchitis that is not very severe, and may be the only symptom in the chronic disease where it is almost invaribly associated with the production of a fair amount of sputum The treatment of this cough must always be accompanied by the treatment of etiological factors of the bronchitis itself The relief of this simple type of cough may be accomplished by mixtures contain

ing small amounts of drugs designed to depress the cough reflex such as codeine, demerol, dicodid, etc—the amount should not exceed ⅛th grain of codeine to the dose, or corresponding amounts of other drugs

In most cases, particularly in acute bronchitis, and, more particularly in the winter time, the use of high humidity atmosphere relieves a great deal of the irritation responsible for the cough This may be obtained by the inhalation of steam or by placing the individual in a room or a tent where the relative humidity approximates 100 per cent Where the condition is not so acute, and the irritation is not so severe, much relief can be secured by the use of devices for increasing the moisture of rooms and maintaining a relative humidity of approximately 50 per cent The steam kettle type of humidifier is quite satisfactory if it does not make the room too warm, but the cold vaporizing apparatus is a much more desirable and pleasant one for most patients It is particularly important that the moisture in the air be maintained during the night The humidifying of sleeping rooms is sometimes all that is necessary to alleviate a cough

Another factor to be borne in mind is that there is frequently, if not always, some allergic component in the bronchitis Consequently, these tickling, irritating coughs will frequently improve with the addition of moderate amounts of antihistaminics These may be added to the cough medicine or given as independent medication

Bronchial secretion is almost always present in these cases and is very frequently the factor that maintains the cough or increases the severity Consequently, any treatment that does not take this secretion into account may be something less than satisfactory Since the secretion is the direct result of an infection and may produce wheeze or dyspnea, its management will be handled under those headings

Acute irritations or overstimulation of the bronchial mechanism may cause the cough to become spasmodic in nature. This is the "choking cough" which the patient talks about, or what he sometimes describes as cough that can not be stopped once it starts This is likewise the croupy cough and may be observed to be a succession of coughs during one expiration followed by rapid, deep inspiration frequently while the larynx, trachea or bronchus is partially obstructed resulting in a crowing or whistling noise This is one of the most troublesome types of cough and must be approached once again by the attack on the etiological factor and by an approach to eliminate the secretion which is always present, as well as an attempt to treat the cough itself

Bearing these other conditions in mind, the treatment of the cough will require medication that is more potent in depressing the reflex than that used for more simple coughs For this, demerol and/or dicodid are the best drugs since they relieve rather than increase the spasm of the bronchus which may occur with the use of morphine or any of its derivatives Bronchial anti-spasmodics are valuable here Atropine or ephedrine are very effective—atropine by its mechanism of blocking the parasympathetic impulses which cause contraction of the bronchi and ephedrine by its stimulation of the sympathetic system causing dilation of the bronchial lumen These may be used separately but are much more effective when used together there being a synergistic action of the two drugs, 1/300 grain of atropine and ⅜ grain of ephedrine used together give a marked anti spasmodic action

Under some circumstances it is more desirable to use drugs by the aerosol route Here epinephrine 1 100, vaponephrin, or isuprel solutions are very effective It is important that these be used as an aerosol and not with an atomizer since this latter instrument produces droplets of too large size to penetrate into the respiratory passages Occasionally, in severe spasm, it may be necessary to use epinephrine by injection *In general it is possible to control the most severe type of wheezing or* bronchial spasms by other methods and is rarely necessary to use this Aminophyllin is a very valuable drug in cases where the wheezing or spasm approaches the asthmatic state

In cases of difficult spasmodic cough that do not respond rapidly to other medications, inhalation of carbon dioxide is most valuable This should be administered as a mixture of 95 per cent oxygen and 5 per cent carbon dioxide to be inhaled by mask for a period of 15 minutes every *hour The mechanism of this is both central and local in action* The resulting increase of carbon dioxide in the blood stream produces stimulation of the respiratory center This causes an increased depth of respiration and thus with deeper inspiration a greater widening *and lengthening of the bronchial tube since the impulse to the respira* tory muscles and to the bronchi is simultaneous Such impulses repeated 20 to 30 times a minute have the effect of abolishing the spasm of the bronchial musculature, thus easing the cough Carbon dioxide also *works locally and directly upon the secretion causing liquefaction and* decrease in viscosity associated with a lowering of the pH Thus spasm is relieved, the irritating secretion becomes thinner and with the increased amount of air reaching the alveoli distal to the bronchial

secretion, the offending substance is much more easily expectorated and thus relieves the necessity of so much coughing

CONTROL OF INFECTION

Although cough is the presenting symptom and therefore the one that must be treated first there is no treatment that is effective that does not attack the etiology directly Since infection is the most common cause, treatment for this will be needed often

In the acute forms of this disease where chills fever, malaise, and other symptoms of recent infection are present, this must be attacked directly In most cases penicillin given by injection will clear up this infection If the organism involved is penicillin resistant, or a virus the use of such antibiotics as aureomycin chloramphenicol or terramycin may be effective These should be given for a period of at least five days although the cough and symptoms may disappear within 24 hours Where temperature is not elevated and in some cases where the condition has lasted a long time or where the cough is very irritating, medication is more effective when given as an aerosol In the long standing case, this is because the infection has gradually been walled off from the blood stream by connective tissue elements The absence of fever and toxic reaction in the patient although infection is present in the bronchi, is evidence of the inability of the toxic material to enter the blood stream This same factor prevents a drug, present in the blood stream, from reaching the infection in the bronchus Therefore the direct topical application of the antibiotic produces the better result Penicillin solution containing 50 000 units per cc may be given four or five times a day when symptoms are severe This will be gradually changed as symptoms improve until the patient is receiving 1 cc of aerosolized solution twice a day, this however to contain 200 000 units penicillin per cc

If there does not seem to be sufficient relief it may be due to the presence of gram negative or other penicillin resistant strains in the bronchi Under such circumstances the addition of 100 milligrams of streptomycin to each cc of the above mentioned solution will generally take care of this As yet neither aureomycin nor chloramphenicol can be used as an aerosol

WHEEZING AND DYSPNEA

One of the most troublesome complaints of bronchitis is bronchial obstruction This may vary from the minor interference of a small

amount of mucus whose only symptom may be an expiratory wheeze to the major obstruction in severe irritation which results in acute respiratory embarrassment

Wheezing is such a common symptom in acute bronchitis that it probably occurs at some time in every case In the ordinary case, this is not a serious occurrence and the treatment of the infection and the cough will generally relieve this also Where allergy is present, the mild wheeze will respond to anti histaminics supplemented by occasional inhalation of bronchial dilators Sometimes medication designed to liquify the sputum is needed In addition to this, as in all cases of bronchial irritation, it is important to pay attention to the humidity of the patient s room, and be sure that this does not drop below the 50 per cent level

In acute irritation, bronchial obstruction may be the most serious symptom This occurs in severe infections, particularly in the laryngo-tracheo-bronchitis of young children and the acute diffuse tracheo-bronchitis of adults It is likewise the picture in acute allergic bronchitis which develops into asthmatic attacks In bronchitis of irritative or traumatic origin, spasm and obstruction are the cardinal clinical signs It is obvious that when possible, the etiological factor must be treated or removed since treatment of the respiratory difficulty in the presence of the disturbing element is at best palliative

Dyspnea caused by obstruction whether or not cyanosis is present should be treated by inhalation of oxygen This is most satisfactorily accomplished by the positive pressure mask An expiratory pressure of four centimeters of water will tend to prevent the closure of the smaller bronchi This not only maintains the airway and maintains the oxygen level in the alveoli by diffusion but tends to alleviate the acute spasm which is always associated with complete closure of the bronchial lumen Where the irritation is severe and respiration is difficult, helium and oxygen mixtures will increase ventilation without proportional increase in muscular effort Since the customary helium oxygen mixture contains 20 per cent of oxygen and 80 per cent helium, the use of an additional oxygen cylinder connected to the helium mixture with a Y tube, may permit the use of higher oxygen percentages It is well to remember that the higher the percentage of oxygen the lower is that of helium and thus the improvement by this lighter gas in ventilation is lost to that extent However, when dyspnea is severe, the need for oxygen is so great that this takes precedence over other situations Frequently the proper

use of a positive pressure mask will make it possible to use 100 per cent oxygen in the most severely obstructed cases

In these cases, all the measures referred to above for the relief of spasmodic coughs should be used since relaxation of the bronchus is important in the establishment of adequate ventilation

The severity of the lesion, although it may originate in the bronchi, invariably produces pulmonary changes The resulting picture is then broncho pulmonary with pneumonia, atelectasis or pulmonary edema, which conditions must be treated as well as the bronchial pathology As in all bronchial irritations, a high humidity atmosphere is important Its importance is accentuated by the severity of the irritation of the bronchial mucosa Consequently, the inhaled atmosphere should be completely saturated with water, or what is even better, normal saline This can be accomplished by a steam room or the whirling type of cold humidifier If oxygen is being used, the addition of a nebulizer in the circuit or other adequate humidifying of the inhaled gas is essential, since dryness even of the normal variety will cause acute spasm and irritation of the bronchi

DRAINAGE

Bronchial secretion is found in all cases of bronchitis and its elimination is essential to a cure In the mild case and in many acute cases, treatment of the cough and etiological factor will be all that is necessary However, in some acute cases and in all chronic cases, the secretion has a tendency to be thick or to thicken progressively so that its elimination becomes a problem This is particularly true in allergic bronchitis and in disturbances of mucous metabolism sometimes called fibrinous bronchitis In these latter two conditions, drainage of secretion is the essential part of treatment since its viscosity may cause the obstruction of bronchi with production of atelectasis or the partial obstruction with subsequent emphysema and bronchiectasis Another reason why the elimination of secretion is important is found in the response of the bronchi to foreign material Secretion being foreign matter causes irritation and irritation causes cough and more secretion Cough produces more irritation and more secretion, and thus, more cough The result is the well known vicious circle which, in this case, must be broken at all three points rather than one since any one of the three is capable of producing the other two

The first essential for drainage is that the bronchi be open This can be secured by the procedures listed above The second requirement is

that that secretion be liquid enough to run through the bronchial tubes The best medication to produce this result is potassium iodide This has been used for many generations as a primary treatment in all bronchial disturbances, and recent work indicates that the faith of the old clinician in the use of this drug in the liquefication of secretion is justified It is excreted from all the cells of the bronchial mucosa with and into the mucopurulent secretion Potassium iodide has a greater effect in liquifying the secretion or in reducing its viscosity than any known drug that can be given safely to patients In cases where, for any reason this cannot be used, ammonium chloride in large amounts may be an adequate substitution The use of aromatic spirits of ammonia is frequently of great assistance This is due, no doubt, to the ammonium ion which diminishes the viscosity of the secretion, and by so doing, seems to loosen it from its adhesion to the bronchial wall The effect of this is that the patient will cough up sputum in chunks within an hour after administration of the medicine

In some cases where the secretion is very viscid more rapid relief may be obtained by using potassium iodide or ammonium chloride solution as aerosols Since both of these substances are irritating in high concentrations, they must be diluted to a point where they do not, of *themselves, cause further irritation to the bronchial tree A solution* of potassium iodide containing 7 grams per 100 cc or ammonium chloride containing 3 to 5 grams per 100 cc will not be distressing The inhalation of 1 cc of these solutions should always be followed by the inhalation of 1 or 2 cc of isotonic solution of sodium chloride, likewise as an aerosol

If the secretion is not too profuse, the normal mechanism of the body will be sufficient to eliminate it However, when there is a great deal of secretion, or when the inflammation is of long standing particularly when it involves the bronchi of the lower lobes postural drainage is necessary to aid in its elimination This procedure is generally considered to be of value in bronchiectasis or lung abscess and is not used often enough in cases of bronchitis It is extremely useful and will frequently make all the difference between adequacy and inadequacy of expectoration of secretion In some cases where the bronchitis is very diffuse and where there is a respectable amount of secretion in all lobes of the lung, postural drainage may not remove all the retained material In such cases drainage may be established satisfactorily by the use of the Sanders oscillating bed This apparatus can be adjusted

so that the head may be lowered as much as desired and the speed of the cycle be decreased A patient placed in such a bed soon acclimates to the motion and becomes very comfortable It is noticeable that after the first 24 hours there is a marked improvement in the cough and in the ease of respiration

These various aspects of treatment (1) management of the cough, (2) control of the infection or other etiological factors, (3) improvement in ventilation and respiration, and (4) establishment of adequate drainage represent the approach to individual problems which occur to a greater or lesser extent in all bronchitis and which may be handled frequently as separate situations However, in the majority of cases, particularly in the severe or the long standing cases, all of these aspects of treatment must be combined to produce a satisfactory result Cough is dependent upon irritation, infection, and secretion Infection can not be cleared up without adequate drainage, the improvement of respiration requires the abolition of infection and drainage of secretion, and drainage, by itself, is of no value if the factor producing secretion continues to function Consequently, there must be a fine balance in treatment so that the patient receives therapy adequate for his case, but is not over treated to a point where the therapy alone continues the disease

Follow Up

If the bronchitis has existed for any considerable period, even a matter of weeks, it is important to watch the patient for some time to prevent recurrence It does not take long to destroy the defense mechanisms of the bronchial tree but the regeneration is slow, like all curative processes When all symptoms are gone, these defenses may yet be absent, and a mild respiratory infection cause a new inflammatory process to begin

Therefore, the patient should be placed on a regimen of adequate rest and diet and all other methods of constitutional building up used For some period of time during and after the symptoms, vitamin adjunctions should be used A larger amount of Vitamin A than usual, 50,000 units a day, is sometimes helpful in these cases Any suspicious beginning cold should be treated immediately and intensively, and all attempts made to avoid such an infection

Preventative measures are at best indefinite Cold vaccines whether oral or parenteral are rather uneven in their effectiveness and of questionable value There are some patients of the chronic bronchial

infection group, who seem to do better with oral vaccines but no definite conclusions can be drawn from this The antihistamine preparations alone or combined with other cold remedies are particularly valuable in preventing recurrences of allergic bronchitis

If any sign of recurrence of bronchitis should occur, the condition should be treated without waiting to see whether it will develop any clinical importance

There are two items that may not be overlooked First that since tobacco smoke is an irritant to the bronchi, producing spasm, inflammation, and secretion, no individual whose bronchitis was at all chronic should be permitted to smoke cigarettes The use of tobacco without inhalation will not be injurious to the bronchi Second, at any time when artificial heat is used, all rooms and especially sleeping rooms should be adequately humidified An inexpensive humidity indicator will show whether a humidification device is necessary If such an apparatus is needed, it is generally more satisfactory to use a cold humidifier rather than one that uses steam

By these means a patient may be kept free of recurrence long enough to rebuild defenses and resistance When this has been attained freedom from bronchitis is possible

BRONCHIOLITIS

Bronchiolitis refers to infection or inflammation of the bronchiole Except in rare instances this is associated with bronchitis In addition to this, bronchiolitis is always associated with an interstitial pneumonitis and *frequently bronchopneumonia* The *etiology* is almost invariably infection which may be bacterial in nature or more commonly associated with one of the viruses It is not definitely known which organisms show a particular predilection for the bronchiole as opposed to the bronchi Such an infection is a common occurrence in influenzas and some atypical pneumonias It is very rarely seen with infections originally caused by pneumococcus, streptococcus, staphylococcus, although these organisms may occur as secondary invaders when bronchiolitis has once been established

The symptoms are generally all out of proportion to the clinically demonstrable pathology Malaise and other evidences of toxicity, accompanied by severe cough, are the most frequent Elevation of temperature occurs early in the disease and, depending upon the organisms involved

may vary from slightly above normal to 103° F The chief symptom is cough

Early in the disease this cough is severe, spasmodic, but non productive It is purely irritative in nature At this time or shortly thereafter the patient may experience pain in one side of the chest, and a wheeze may occur on deep expiration It is at this time that the infection has extended into the interalveolar area with the production of interstitial pneumonitis Examination of the patient will show altered breath sounds in this area of the chest Fine rales are very rarely heard, since the alveoli are not involved except as a secondary change Roughened breathing, medium rales, and expiration wheeze are the customary findings It is noteworthy that on routine fluoroscopy and x ray film, the chest may be considered negative On careful examination, however, fluoroscopy may show some diminution of diaphragmatic motion and expansion of the involved region of the lung and an x ray film with sufficient detail may show some fuzziness along the blood vessel markings in contrast to the clarity of those in the opposite lung This fuzziness is caused by the inflamed areas in the small bronchioles and contiguous tissue The diagnosis is made clinically on the clinical picture and the physical findings

Treatment must be directed at the infection Antibiotic therapy is the method of choice, and those of the aureomycin, chloromycetin, and terramycin type the most desirable If this is started early in the disease, it will frequently alleviate the cough rapidly without further therapy If this does not occur or if the symptoms are sufficiently severe, the cough should be handled according to the principles and treatment of severe spasmodic and non productive cough, discussed in the section on the treatment of cough

It is very important to follow the course of the patient, both by physical examination and x ray, because the alleviation of symptoms by antibiotic therapy may mask the continuation of a disease process Furthermore, all of these symptoms, in fact actual infection of the small bronchi may be associated with a foreign body or tumor or other cause of bronchial obstruction Therefore, when a patient does not improve rapidly and completely, bronchoscopy should be done

Course This is a disease that needs treatment It shows great tendency to chronicity and if left alone may result in breakdown of the walls of the bronchiole and the small bronchi with the eventual production of bronchiectasis It should never be allowed to go into this chronic state but if for any reason chronicity has been established the bronchial and

bronchiolar infections should be treated extensively with aerosol and systemic antibiotics and the cough managed with antispasmodic cough mixtures until all symptoms have disappeared

BRONCHIECTASIS*

By CHARLES M HENDRICKS, M D

Introduction

Bronchiectasis is not a primary disease It occurs only as a sequel to, or a complication of, a prior bronchial or broncho-pulmonary disease or accident. It is a complex disease initiated by a chain of events such as bronchial obstruction, the resultant atelectasis, and others

The disease was first described by Laennec after one of his assistants had called his attention to the condition in 1808 From that time until the discovery of the diagnostic use of iodized oil in 1922, the disease was considered a rare condition However, since bronchographic studies have been made possible, more and more cases are being discovered until now in some localities in the United States the disease is recognized more commonly than pulmonary tuberculosis

The true incidence of the disease is not as yet reflected by statistics The disease may develop in an individual of any age, and is no more prevalent in one sex than in the other With the ever increasing number of cases being discovered, interested observers have studied groups of cases, and in many instances their findings differ and therefore many theories as to the pathogenesis have been developed The main reason for the variation in findings is simply due to the natural variations in the different stages of the disease studied by these workers

Changing concepts of pathogenesis may be noted in each new discussion on the subject Because the development of the disease is dependent on so many complex factors, it is doubtful whether all the facts and factors have as yet been definitely established and placed in their proper relationship For this reason, the pathogenesis of this disease remains controversial

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*Bronchiectasis is a word used to define a dilatation of any part of the bronchial tree
*Bronchiectasis is a word also used to define a chronic broncho-pulmonary disease characterized by a bronchial dilation accompanied by infection

describes a deformity and becomes Diverticulitis when symptoms appear Therefore, it would be less confusing no doubt, to speak of "Bronchiectasis" when we have in mind a deformity of any part of the bronchial tree, and "Bronchiectitis when we have in mind this particular broncho-pulmonary disease

Etiology

In the past decade, great advances have been made toward a complete understanding of the etiology of this disease The correlation of data obtained from case records, bronchograms, bronchoscopic studies, pathological studies of necropsy cases, as well as recently removed lobes and more recently increased interest in bacteriological studies, have thrown a new light on the development of the disease

Etiological factors such as paranasal sinusitis, congenital and prenatal conditions in the past were considered of primary importance by many, while recent discussions on etiology only mention these factors in passing Many observers still believe that sinusitis plays a great role Recent studies, however, indicate that sinusitis is not necessarily associated with all cases of bronchiectasis While the two diseases do occur simultaneously in the same patient, there are hundreds of cases of bronchiectasis in which sinusitis, tonsillitis, and other upper respiratory infections could play an important part in etiology, however these factors are of much less importance than acute broncho-pulmonary infections Today, most observers agree that the two prime etiological factors are bronchial obstruction and pulmonary infection They also agree that many other factors may enter into etiology, but from a practical standpoint these two significant etiological factors are paramount

Congenital Bronchiectasis

That prenatal and congenital conditions contribute to the establishment of bronchiectasis is still an open question One group of observers believe these conditions are of major importance in the production of the disease, while others feel they contribute little, if anything, to the etiology Then there is the middle road group of observers who believe that antenatal anomalies are real etiological factors, although rare because of the following well known facts

Anatomical (symptomless) bronchiectasis (dry bronchiectasis) is found during life by the use of a bronchogram, also, at post mortem examination anatomical bronchiectasis is found in persons dying from other causes. This appears to be definite proof that anatomical, uninfected bronchiectasis does exist and only becomes a clinical disease after interrupted drainage and infection The most recent writers on this subject believe, however, that we are more liable to find on close study that infants usually acquire bronchiectasis Congenital cystic

disease, an important congenital abnormality, is an unusual occurrence, but its existence can not be denied It is possible, however, that a diagnosis of cystic disease is quite often made when in fact in many cases the condition is actually acquired bronchiectasis Aspiration pneumonia may occur on the first day of life when amniotic fluid is aspirated into the lung tissue This does occur with a fair degree of frequency, and is most common among those infants who have anoxia during delivery *This is a serious condition and many infants succumb* after a few days or weeks In cases that recover, bronchiectasis may occur as a result of atelectasis following the blocking of one or more bronchi While it is possible for a child to be born with one or more dilated bronchial tubes, and while cases have been reported in which

Acquired Bronchiectasis

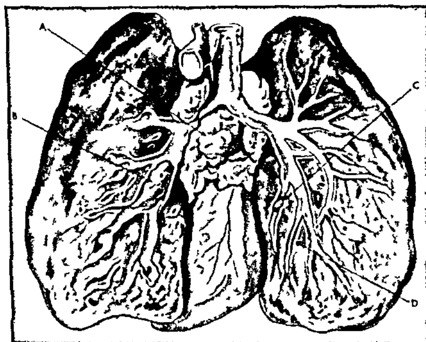


Fig 1 Illustrates four causes of bronchial obstruction (a) Obstruction of the main bronchus due to pressure of a growing tumor outside the bronchus (b) Intrabronchial obstruction due to adenoma (c) Intrabronchial obstruction by foreign body (peanut) (d) Intrabronchial obstruction due to an acute inflammatory process.

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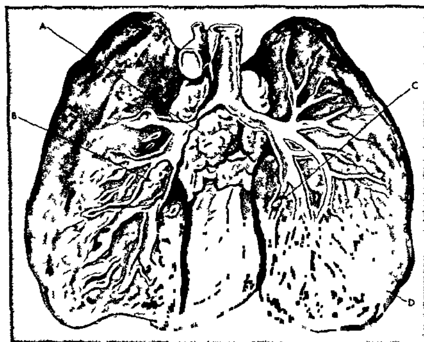


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transposition of viscera is associated with bronchiectasis, and there has been established in rare instances a relationship between cystic fibrosis of the pancreas and bronchiectasis, it must be admitted that all these conditions are rare

It is now safe to say that by far the vast majority of cases of bronchiectasis in infancy and childhood are acquired

Since it is now believed that bronchial obstruction and pulmonary infection are the two most important etiological factors in acquired bronchiectasis, we will discuss obstruction first

In childhood, obstruction may result from plugging of bronchi with a foreign body, inhaled objects of all sorts, including particles of food, tenacious mucus or from the inflamed and edematous bronchial mucosa resulting from acute infection Obstruction may result from most of the common respiratory infections such as pneumonia and bronchopneumonia, either alone or as a complication of measles, whooping cough, or influenza It has been reported that from 73 to 85 per cent of the cases of bronchiectasis in children follow the above named acute diseases

In adults, acquired bronchiectasis develops following obstruction resulting from any acute respiratory disease such as pneumonia, *bronchopneumonia, acute bronchitis, plugging of bronchi by foreign* body such as broncholiths, dental accidents, or the aspiration of small objects which may occur among workers in various industries Obstruction may occur from the inhalation of certain war gases, especially mustard gas In such cases, pathological changes begin with an acute chemical irritation or burn of the bronchial mucosa, followed by ulceration and secondary infection Obstruction may also occur from pressure of lymph nodes or tumors outside the bronchus or neoplasms within the bronchus Fibrosis from any cause such as pulmonary tuberculosis, silicosis, lung abscess, chronic empyema, asthma and emphysema, may produce a stenosis or complete obstruction of the bronchus resulting eventually in bronchiectasis

Bronchiectasis also occurs in many instances in the lower lobe following thoracoplasty The obstruction in acquired bronchiectasis may be sudden or may be a gradual process In either case, the result is reduced aeration of the corresponding lung segment with partial or complete atelectasis of this segment

Dilation

What roles do these two factors, namely, obstruction and infection, play in the production of the dilation of a bronchus? If the obstruction is due to a foreign body, an adenoma, or a slow growing cancer within the bronchus, or to pressure from a neoplasm, an enlarged lymph node, or to fibrosis of lung tissue, secretions will be retained, become stagnant, and finally infected The most frequent cause of obstruction, however, is infection. When the lumen of a bronchus is inflamed and its mucosa swollen, due to infection, allergy, or the inhalation of corrosive gases, or if the obstruction is due to a plug of purulent mucus, the same phenomenon prevails, namely, the accumulation of secretions which become stagnant and are either already infected or will become infected later, because in an obstructed bronchus the normal protective agencies, namely ciliary motion, peristaltic motion, and reflex cough mechanism no longer function, thus contributing to increased bacterial growth In both instances, obstruction per se is followed by infection, and then the pathological process producing dilation proceeds as follows The infection spreads into the bronchial wall and the immediate lung parenchyma, producing destruction and scar tissue The elastic tissue is destroyed and replaced by newly formed scar tissue which is gelatinous and easily stretched by inspiration and the weight of the retained secretion When complete obstruction occurs, atelectasis of the primary lobules or lung units of the related pulmonary area occurs This also aids in the dilation process by the loss of elastic support of the air filled alveoli, and by the pulling effect of the intrapleural negative pressure

The dilation may be diffuse or localized If localized, we speak of the dilation as saccular If diffuse, it is commonly called cylindrical Bronchiectasis is bilateral in 50 per cent or more of the cases The lower lobes are more frequently involved, because of retained secretions due to gravity However, bronchiectasis may occur in the upper lobes and in the middle lobe of the right lung Bronchiectasis occurring in the middle lobe of the right lung is sometimes spoken of as "middle lobe syndrome" The size of the bronchial dilation depends on the caliber of the bronchus infected Every element of the bronchial wall is frequently destroyed The lobe or lobes involved are contracted and firm The bronchi are more or less bunched together, and the mucosa is covered by purulent exudate Occasionally small dilations are found which contain cheesy masses This is the result of a complete obstruction which

Morbid Anatomy



Fig 2 (a) Saccular type of dilation (b) Grapelike dilation or small saccular type (c) Fusiform type (d) Cylindrical type

remained complete following the onset of the inflammatory processes in this particular bronchus In the majority of instances, drainage from the dilation has been reestablished following the initial acute partial or complete obstruction The lung parenchyma associated with and immediately adjoining the bronchial dilation is composed of inflammatory tissue which may contain areas of necrosis, especially in advanced cases Naturally, the variation in gross appearance is due to the severity of infection and amount of involvement In far advanced cases, extensive adhesions between the infected lobe, the chest wall and the diaphragm may be found The lingula of the upper left lobe is frequently involved As yet a satisfactory explanation of this fact has not been found

Occasionally an anatomical dilation may be found which is not associated with any apparent past infection These dilations are sometimes found accidentally by bronchogram They occur most often in one of the upper lobes or the middle lobe This type of dilation never produces symptoms unless it becomes infected Occasionally one finds a dilation, the mucous membrane of which contains varices, and from which hemorrhages may occur Most pathologists refer to both types described above as ' dry bronchiectasis ' Hemorrhages are not uncom

mon in the type where varices occur The only explanation for this condition, a dilation with varices, is that there has been a spontaneous cure of the infectious process which produced a dilated bronchus with the remaining pathological condition, namely, varices

Histopathology

Here again the findings are dependent on the stage and severity of the disease Sections taken from involved bronchial areas usually show chronic abscess formation The first stage of this inflammatory process shows the epithelium apparently floating over seropurulent exudate, separating the epithelium from the basal membrane The next histological change is one of desquamation of the epithelium which leaves a denuded area in the bronchial wall Later the exudate fills the bronchial lumen The exudate quite often contains remnants of the desquamated epithelium Sections of later stages show that the adjacent alveoli are involved in the same type of inflammatory process Other sections of the advancing inflammation as a result of infection, show necrotic processes which destroy the main elements of the normal bronchial tissue, which, in turn, is followed by a process of repair The destroyed bronchial wall being replaced by fibrous tissues and in most instances the desquamated epithelium is replaced by nonciliated epithelium The adjacent parenchyma shows fibrosis with intervening collapsed alveoli Sections of tissue from these involved areas most usually show gram positive cocci, morphologically pneumococci, streptococci and staphylococci These bacteria probably represent the etiological factor in most cases

Diagnosis

Any one seeking medical advice concerning a productive cough, who gives a history of having had pneumonia, bronchopneumonia, influenza, whooping cough, tonsillitis or sinusitis, or if the person has any deformity of the thoracic wall or compression of lung by pneumothorax, pleural effusion, or surgery, he should be examined for bronchiectasis X-ray studies of the chest are essential, especially bronchograms should be depended upon In the plain postero anterior films, the presence of bronchiectasis is suggested by the hilar density on the affected side, with increased markings extending into the middle zone and bases of the lung In young children, one of the characteristic findings is the presence of a triangular shadow at one or both bases The hypotenuse of the

triangle extends from the hilus to the costal margin At operation, these triangular areas prove to be due to atelectic changes Occasionally, these triangular areas are not due to atelectasis but are the result of mediastinal pleurisy and malformation associated with the spine, aorta, esophagus or vena cava

Symptoms vary greatly from none to severe, depending on the amount and severity of infection

Cough is the rule and occurs in paroxysms, usually at long intervals, almost always on the patient s waking in the morning The severity and number of paroxysms depend on the severity of the disease

Expectoration In mild cases there may be little or no sputum The amount of sputum increases with the severity and extent of the disease In some cases, the amount of sputum may be as much as three pints in 24 hours The attacks of coughing are usually attended by expectoration The sputum is usually purulent in character and may be foul smelling Fetid sputum occurs in about 25 per cent of the cases The odor may be extremely disagreeable, so that the patient's breath may be perceived some distance away These patients are practically ostracized socially and are often unable to hold any position which requires their contact with others If the sputum is collected in a glass and allowed to stand, it will separate into three distinct layers The top layer is a frothy foam, the middle layer is a thin, almost serous fluid, and the lower layer is thick, purulent, and contains conglomerated masses The latter appear as dirty yellow, varying in size from a mustard seed to a bean

Hemorrhage Hemorrhage is a very prominent symptom of bronchiectasis and occurs more often than in pulmonary tuberculosis In bronchiectasis, the hemoptysis is most often due to bleeding granulation tissue involving the bronchial mucosa Occasionally, hemorrhages are from varices in so called dry bronchiectasis

Fever Many patients with bronchiectasis have what is commonly called acute exacerbation of pneumonitis and pleurisy accompanied by fever, chills, and night sweats Some of the attacks may be true pneumonia, while a great majority are usually the result of acute recurrent infections added to the already chronic suppurative process

Physical Signs

Inspection Findings on inspection will vary with the extent and severity of the disease The color of the skin is usually unchanged When bronchiectasis is confined to one side, the patient usually lies upon the

affected side Deformities of the thorax are rare and occur only in the case of retraction of the lung or when extensive pleural adhesions are associated with bronchiectasis If emphysema is present, the thorax may show the characteristic barrel form There may be lagging over the lung area most affected Clubbing of fingers may be found in long standing cases

Palpation Fremitus may be increased if there is extensive pulmonary fibrosis, provided the fibrosis extends well into the periphery If the pleura is thickened, fremitus may be absent or decreased Fremitus may be decreased in cases of emphysema complicating the disease

Percussion The percussion note in bronchiectasis varies greatly, depending upon the size of the dilations and quantity of fluid present and its distance from the chest wall and character of change in the surrounding lung tissue Dullness or a tympanitic note may be obtained, each one alternately, depending on whether the small cavities and bronchi contain fluid or air Dullness will be the rule over marked fibrotic areas and thickened pleura Hyperresonance will be found over emphysematous areas

Auscultation In many mild cases no abnormal sounds will be heard In others, fine and moderately coarse rales may be heard over the diseased lobe Quite often rales will be heard one day over a certain lung area, and on the next day these rales will not be heard This depends, of course, on whether or not the contents of the bronchi have been evacuated

The Bronchogram

Bronchographic study is accomplished by the instillation of iodized oil into the bronchi In all cases postural drainage of the bronchi should be accomplished prior to the instillation of the oil In some cases it may be necessary for the bronchoscopist to withdraw with suction the contents of the dilated bronchi prior to instilling iodized oil in order to secure a satisfactory bronchogram A patient should be especially prepared and certain precautions should be taken before the instillation of the iodized oil The patient should be tested for sensitivity to the three oils used as a base for the iodine, namely, peanut oil, poppy seed oil, and sesame oil If the patient is known to be sensitive to iodine, brominized oil should be used instead The patient s stomach should be empty If he is extremely nervous, a sedative should be employed half an hour before the examination Iodized oil should not be instilled or the employ-

ment of cocaine or its dirivatives should not be done until careful inquiry to the patient s sensitivity to such drugs has been determined Severe reactions have been noted, and death has occurred in a few cases Iodized oil should not be instilled into the bronchial tract in the presence of known bronchial obstruction, especially if difficult breathing is present Neither should it be instilled in cases with acute exacerbations

After all precautions have been taken, the pharynx and larynx are sprayed or swabbed with 5 per cent cocaine or 2 per cent solution of butyn A few drops of the anesthetic should be instilled into the trachea a little at a time, until the cough reflex disappears Usually between fifteen and twenty cc of iodized oil are necessary for a satisfactory bronchogram of one lung In order to produce a satisfactory bronchogram of the right lower lobe, the patient sits upright and leans slightly to the right, for the left lower lobe, the patient should lean far to the left, because of the increased horizontal position of the left bronchus In order to instill oil into the middle and upper parts of the bronchial tree, the patient must be placed in such a position that the oil will gravitate into the desired lobe or lobes

Fluoroscopic examinations should be made prior to and after the instillation of the iodized oil, at which time the condition of the heart and the mediastinum and the position and action of the diaphragm may be observed Fluoroscopic examination should be made from all angles of the chest in order to determine whether sufficient oil has entered that portion of the bronchial tree to be studied, and whether any great amount of oil has been swallowed X ray films, 14x17, postero anterior, stereoscopic, lateral and oblique flat films should be made in each case after the instillation of the iodized oil

The difference between an ordinary roentgenogram and one taken with the assistance of iodized oil in the case of bronchiectasis needs to be seen to be appreciated The most prominent findings are the dilated bronchi brought out by the accumulation of the iodized oil within the lumen of the bronchi One can easily visualize the cylindrical and saccular types Some roentgenologists have described these iodized oil filled spaces as saccular type, grape like dilations, fusiform dilations, and cylindrical type dilations with club like termination The morphological changes have been known to pathologists for years, but the introduction of bronchography makes clinical diagnosis possible The size and shape of the dilations do not influence the symptoms or prognosis or the treatment The vast majority of dilations are cylindrical

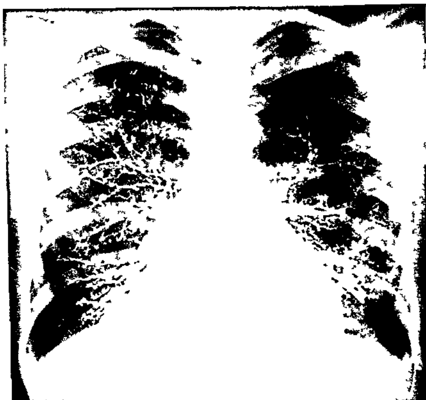


Fig 3A Postero anterior bronchogram shows the definite saccular type of bron chietas s characterized by shadows showing pools of iod zed o l

In some cases the bronchi may show little dilation on the bronchogram, despite the presence of extensive disease, because pathological studies have shown that fibrous contraction takes place around dilated spaces during reparative stages of the disease Therefore, the bronchogram should not compel a negative diagnosis in the presence of all classical symptoms

Bronchoscopy

Bronchiectatic dilations are seldom seen through the bronchoscope, because the disease occurs in the smaller bronchi which are generally inaccessible to bronchoscopic examination However, bronchoscopy is very important in investigation of bronchial lesions, many of which are responsible for the dilatation In each case of unilateral bronchiectasis,



Fig 3B Lateral view same patient shows even larger pools of iodized oil in the lower left lobe

bronchoscopic examinations have been made for possible bronchogenic tumor, extrinsic stenosis, foreign body or tuberculosis Bronchoscopy is a valuable aid in localizing the disease by observing the orifices from which the exudate is discharged It is also of valuable assistance is securing uncontaminated specimens of the exudate for culture It is often advisable to perform bronchoscopy before bronchography, in order to be certain that all bronchi are not obstructed with secretions If

excessive secretions are present, they should be removed by suction If this is not done, the instilled iodized oil will fail to enter many ramifications in the bronchial tree and a true and accurate picture of the condition suspected will not be obtained Bronchoscopy may also be valuable in the treatment of bronchiectasis by the removal of a foreign body when present, and in cases where bronchostenosis exists Dilations of the stenotic area are usually followed by improvement When cases of benign tumor of the bronchus are discovered improvement is the rule following the removal of the tumor

Bacteriology

Most observers who have written on this subject have stated correctly that there is no specific organism responsible for the disease Many, however, have pointed out that fusiform bacilli and spirochetes are quite important Later studies show that these organisms have seldom been found in sputum of infants and small children when recovered through the bronchoscope In a careful study of the bacteriologic findings of a hundred adult cases we found only a few fusiform bacilli by culture on potato extract media and it is believed that these occurred because of poor mouth hygiene In the past most writers have not considered bacteriologic findings of any great importance Since the introduction of antibiotics it has been found that a more complete understanding of the underlying infection is necessary Even before antibiotics were employed in treatment studies of the sputum obtained by the bronchoscopic method showed in many cases an ever changing bacterial flora

Now that penicillin soluthricin streptomycin aureomycin bacitracin and terramycin are successfully used as aerosols in the treatment of disease it is found that in many instances certain strains of staphylococcus, streptococcus and pneumococcus all gram positive organisms, are resistant to one or the other of the above antibiotics For this reason bacteriological studies by culture and inhibitive tests are necessary in order that the proper antibiotics be used in combatting these resistant strains Studies as of this date have proved that aureomycin and bacitracin have the widest range antibiotic action of any of the above

It is just as important to make a complete study of the gram negative organisms which seem to increase in number in the sputum of these cases after the gram positive organisms have been reduced or disappear entirely from the sputum Many of the gram negative organisms have

for years been classified as nonpathogenic It is now believed that many of the so called nonpathogenic organisms contribute to the chronicity of the disease Besides the gram-negative organisms listed below, there are many gram-negative cocci and bacilli found in the sputum of these patients that have not yet been classified

Classification of More Important Pathogenic Bacteria Found in Bronchiectasis Sputum, with Gram's Stain

Gram-Positive *(Retain the gentian violet)*	Gram-Negative *(Take color of counterstain)*
Streptococcus hemolyticus	Micrococcus catarrhalis
Streptococcus nonhemolyticus	Bacterium coli
Streptococcus viridans	Bacterium aerogenes
Staphylococcus aureus	Proteus
Staphylococcus hemolyticus aureus	Friedlander s bacillus
Staphylococcus albus	Bacillus pyocyaneus
Bacillus subtilis	Bacillus influenzae
Pneumococci (all types)	Bacillus mallei
Diphtheroids	Gram-Negative Fungi
Many actinomycetes	
Bacillus tuberculosis and other acid fast bacteria	Monilia albicans
	Actinomyces bovis
	Coccidioides immitis
	Occasionally the above fungi are found

Complications

Pneumonitis Acute exacerbations are the most frequent complications of bronchiectasis They may be mild and are characterized by chills, fever, dyspnea, suppressed expectoration, followed by copious amounts of sputum These attacks last only a few days These exacerbations may be mild or severe There is another type of exacerbation which has all the features of *chronic pneumonitis* In this type of exacerbation there is a subfebrile temperature, increased toxemia, increased cough and expectoration with progressive deterioration, usually terminating in acute pneumonia

When secondary changes in the kidneys and heart are not present, the general condition of the patient may be quite good or fair over a

period of years In others, however, *amyloid degeneration* of the kidneys, spleen and liver will eventually occur This condition, while grave, is considered by some to be a reversible process if the primary disease is eradicated, in the case of bronchiectasis, eradicated by surgery

Empyema Empyema may occur as a result of a saccular abscess in the periphery, perforating the visceral pleura, thus infecting the pleural cavity

Arthritis and *pulmonary osteoarthropathy* are common complications

Cor Pulmonale This condition has been described as secondary to chronic pulmonary fibrosis and may occur in bronchiectasis, depending upon the extent of pulmonary involvement Cardiac failure is also described as a complication of bronchiectasis, emphasized by right heart strain

Cerebral abscess occurs as a metastatic lesion and while it does not occur often, it is likely to be fatal It may occur as a single lesion with localized neurological signs, or as multiple lesions with the signs and symptoms of meningitis

In long standing cases, pulmonary fibrosis and emphysema are inevitable

Differential Diagnosis

Since bronchiectasis in the early stages may be characterized by irregular fever and considerable expectoration, the mistaken diagnosis of tuberculosis *has no doubt been made in thousands of cases* However, with persistent cough and expectoration continuing for quite a while after the fever has disappeared, should suggest bronchiectasis In order to rule out pulmonary tuberculosis, the sputum should be examined microscopically for tubercle bacilli and if not found, the sputum should be cultured It should not be difficult to differentiate between bronchiectasis and pulmonary tuberculosis, since we can secure almost conclusive evidence by bronchographic studies of the chest Pulmonary hemorrhage occurs in about 40 per cent of all cases of bronchiectasis It is rather the rule in dry bronchiectasis, which usually occurs in the middle lobe of the right lung Since hemoptysis frequently occurs in mitral stenosis, it is necessary to inquire deeply into the history as to rheumatic fever, or the symptoms of any heart disease, in order to clarify diagnosis In well advanced cases of bronchiectasis, it should be relatively simple to avoid confusion with any other pulmonary condition such as lung abscess and

the various fungus infections Careful studies of the sputum by culture, and of the lung fields by bronchography should clarify the situation

Treatment

Surgical Surgical removal of the affected segment or lobe, or the removal of the entire lung is the only sure cure in carefully selected cases Surgical treatment in the care of bronchiectasis is now thoroughly established, since the mortality rate from surgery has been reduced from 50 per cent to less than three per cent Thoracic surgeons select their cases as follows The age should be preferably under forty, the disease should be unilateral, the general state of health should be good, the diagnosis must be definitely established It is a well known fact that children tolerate lung resection better than adults

Pulmonary function in younger individuals can be estimated by careful physical and x-ray examinations, the vital capacity tests, graded exercise response and other methods Thoracic surgeons now take into consideration the patient's age, the extent of the disease and the cardiorespiratory reserve If the patient is 40 to 45, it is advisable to develop the status of pulmonary reserve, especially if pneumonectomy is planned Most cases of bronchiectasis will pass through a stage when surgery, if performed, would have insured the patient's future health Surgery is often postponed until the stage of the disease has advanced too far for surgery Physicians should recognize the fact that every case of bronchiectasis, once the diagnosis has been proved, no matter how mild the symptoms, may eventually become totally incapacitated

Medical At present the great majority of patients with bronchiectasis usually are too far advanced for surgery, while many others who may be ideal cases for surgical cure refuse operation Therefore, palliative treatment must be afforded these unfortunate people The keystone of medical treatment is postural drainage, however there is a great percentage of these patients who cannot accomplish postural drainage successfully In far advanced cases, many patients have found from their own experience the best position to assume in emptying their lungs In others, because of a fear complex, it is impossible for them to assume the necessary position, which requires the lowering of the head below the level of the base of the lungs It is a natural human trait during a paroxysm of coughing for the patient to assume the upright position, which of course hampers drainage By exercising a great deal of patience and careful instruction, the fear complex in many of these people may

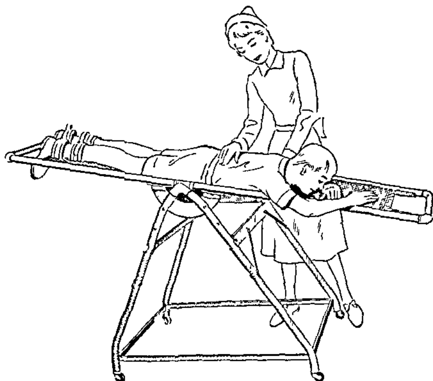


Fig 4 Singer's postural drainage bed This unique table devised by Singer affords the patient the benefit of proper position at any angle the angles controlled by nurse moving levers and ratchets

be overcome Postural drainage, of course is a successful palliative measure, and is accomplished by using the force of gravity The patient may be placed in bed with the foot elevated, or he may place himself on a chair, head down and hands on the floor A unique bed devised by Singer affords the patient the benefit of the proper position by moving levers and ratchets on the bed Drainage should be accomplished twice a day, morning and evening Now and then it will be necessary to employ bronchoscopic drainage when postural drainage fails The general health of the patient must be fortified by the use of vitamins, iron and liver when necessary In the past, many procedures and drugs have been employed, including x ray Over the years observers have found that drug therapy is of little value in the treatment of this disease, and many believe that x ray treatments are harmful As a palliative

measure, expectorants may be helpful in some cases Occasionally a patient receives prolonged temporary relief following the instillation of iodized oil The administration of sulfonamides and penicillin should be employed during exacerbations Expectoration may be facilitated by the use of aerosol bronchodilators and the inhalation of carbon dioxide 5



Fig 5 This picture illustrates how two patients can receive aerosol antibiotics at the same time by the attachment of two gauges on one cylinder of oxygen Instead of the Y tube a special clamp is used Patient compresses the clamp with thumb and finger allowing a free flow of oxygen during inspiration and allows clamp to automatically close during expiration thus conserving oxygen

per cent with oxygen 95 per cent The inhalation of the above liquifies the secretions and aids materially in clearing the bronchial tract

The use of certain chemicals and antibiotic aerosols has become widespread and has proved to be of great value as a palliative measure The first compound used in this manner was a 5 per cent solution of sodium sulfathiazole Later, when penicillin became available, it came

to be widely used as an aerosol treatment of not only bronchiectasis and lung abscess, but all acute respiratory infections It was found, however that not a few patients are allergic to penicillin or may become allergic following continued use This writer has found that tyrothricin, 500 to 700 micrograms per cc is just as efficient as penicillin and in some cases more efficient We have successfully used it in one hundred cases who were allergic to penicillin and only two cases showed any allergy to tyrothricin The newer preparation known as soluthricin may also be used as an aerosol

Since the introduction of penicillin aerosol and other antibiotic aerosols, it has been found that these antibiotics in most cases control the gram positive organisms but there are myriads of gram negative organisms which persist in the patient s sputum For this reason many observers advocate the combination of penicillin with streptomycin, as streptomycin is antibiotic not only to certain gram positive organisms but it is also antibiotic to many aggravating gram negative organisms

It is known that penicillin and streptomycin are synergistic In combining various antibiotics one should be sure that they are synergistic It is quite possible that in combining antibiotics which are not synergistic one will interfere with the bacteriostatic action of the other and vice versa It has already been shown in vitro that the combination of certain of these antibiotics and chemicals interferes with the efficiency of one another It has been shown in vivo that the inhibitory effect of phthalysulfathiazole on aerobacter aerogenes in the human intestine is reversed by parenterally administered penicillin

With the number of antibiotics now available the bacterial content of the sputum should be studied by culture, and inhibitive tests made in order to determine the most effective antibiotic We now believe that aerosol therapy should be continued off and on throughout the lifetime of the patient, as we have seen many advanced bilateral cases who were completely incapacitated and others who lost a great deal of time because of exacerbations improve to the extent that both types of cases are now working full time However these patients continue their aerosol treatments at home, usually night and morning The fear on the part of many physicians who use penicillin aerosol exclusively that the gram positive organisms will become resistant to penicillin after continued use may be well founded since many use only five, ten and fifteen thousand units per cc We have found that 100 000 units given twice daily over a period of months if necessary have probably pre

vented organisms from becoming resistant because of the overwhelming dose As yet we have found no resistant organism in the sputum of any patients that were not resistant from the beginning There are many observers who believe that a definite blood level is a necessary measure of *topical effectiveness of antibiotics It has been satisfactorily shown* that soluthricin as an aerosol is practically as efficient as penicillin although blood levels can not be estimated It has been shown also that satisfactory clinical results are obtained when there are no appreciable penicillin levels in the blood The clinical course is by far the best criterion of the local effectiveness of any antibiotic aerosol The response to aerosol therapy in many instances is dramatic The fever, when present, subsides the amount of sputum is diminished and in many cases entirely absent Unfortunately, however, the effects of antibiotics are not permanent In most cases all symptoms reappear a short time after the discontinuance of the antibiotic For this reason aerosol treatments should be continued indefinitely, switching the antibiotic according to the bacterial content of the sputum obtained by culture and inhibitive tests In this way, the sputum may be changed from mucopurulent to mucoid When this occurs the maximum effect to be expected from aerosol therapy will have been attained

Because of the fact that some of the antibiotics produce oedema of the lips or mucosa of the mouth and sore tongue, it is advisable to have the patient rinse the mouth thoroughly with plain saline water, thus removing the excess antibiotic from the tongue

Postural drainage has been emphasized in another paragraph and should be practiced before each aerosol treatment otherwise much of the antibiotic mist will be lost through expectoration The patient should be carefully instructed to breathe slightly deeper than normal inhaling slowly and at the end of each inhalation hold the breath for a few seconds then exhale through the nose If the patient will follow this routine the antibiotic mist will not be exhaled and lost

Thoracic surgeons have reported that in the preparation of their patients for lobectomies the employment of penicillin or other antibiotic aerosols has resulted in fewer complications and hastened recovery after operation

Prognosis

There is a wide difference of opinion as to the duration of life of patients with bronchiectasis Many observers make the statement that

these patients may live from one to 50 years, which is no doubt true The evident reason for this observation depends upon the degree of pulmonary infection with dilation It is believed that the extent or size of dilations plays no part, but rather the type of infection and rapidity of extension determine the length of life of the individual

Many individuals manage to live a normal span of life, however, in most cases their existence is miserable because of the inevitable periodic exacerbations There are many besides those who are totally incapacitated, who are extremely uncomfortable with pleurisy pains, pulmonary hemorrhages, superimposed respiratory infections, and some develop asthma Chronic cough with foul expectoration socially ostracizes at least 25 per cent of these cases It has been noted that if bronchiectasis occurs during the first decade of life, few will be living after the age of 40 In well established cases of bronchiectasis, only 25 per cent will be able to work full time

Many cases of bronchiectasis develop complications due to intercurrent infections, and thus hasten the advancement of the disease Many patients who might otherwise have survived succumb to intercurrent diseases Since it is believed that the great majority of cases follow bronchopneumonia in childhood, it is likely that the number of these patients past the fourth decade is small The older age group evidently acquire the disease in later life, and when discoverd it is usually of recent origin The available statistics on prognosis leave no doubt of the malignant course of the disease The prognosis among persons with dry bronchiectasis is good

Prevention

Since bronchiectasis is nearly always secondary to some other condition, its prevention naturally would depend on careful attention to the lungs and bronchi of every patient recovering from a respiratory disease Any acute or chronic infection of the respiratory tract, as well as some accidents, may create a predisposing state Now that influenza and whooping cough vaccine are available, the prevention of these two diseases will contribute much toward prevention of bronchiectasis in children Much can be accomplished in prevention among patients recovering from measles, whooping cough, influenza, pneumonia, or bronchopneumonia, by continuously anticipating and watching for the first sign of bronchial obstruction associated with atelectasis The physical evidence of bronchial obstruction is a persistent cough with wheezes

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heard over a given area on auscultation If these findings cannot be satisfactorily explained, they are an indication for x ray study and possible bronchoscopy The early removal of any obstruction such as a foreign body and mucus plugs is an essential preventative measure The early and adequate treatment of acute infections of the respiratory tract is essential In this day of antibiotics, because of their almost spectacular effect on clinical symptoms the tendency is to discontinue their use too early It must be emphasized that they should be continued well through the convalescence X ray inspection of the chest should never be spared and should be made as a routine procedure before discharge from the physician s care Recently, antibiotic aerosols have come into use, and it is believed they will find their place as a preventative measure by their use in each case of slow convalescence, whether or not x ray has revealed the presence of obstruction and atelectasis Certainly they should be used in every case of subacute or chronic bronchitis The awareness of the significance of respiratory infections in infancy and even in adults will save thousands from becoming lung cripples Therefore prevention depends upon the vigilance of the physician and use of all measures now at hand

A consolidated summary of findings and results of aerosol treatment in *100* adult cases of bronchiectasis All cases were confirmed by bronchogram

Age Group	20 30		30 40		40 50		50 60		60-70		70-80	
Male and Female	M	F	M	F	M	F	M	F	M	F	M	F
	10	11	5	13	17	10	14	8	8	2	2	
Predisposing Disease Pneumonia	4	6	2	2	3	5	8	5	3	1		
Bronchopneumonia	1	2	1	7	2	1	4	1		1	1	
Influenza				1	5	1	2		1			
Chronic Bronchitis					1	1		1	1			
Asthma				1					1			
Pulmonary Tuberculosis (arrested)			2					1	1			
Streptococcic Throat Infection	1											
Sarcoidosis	1											
Pulmonary Hemorrhage		1		1								
Thoracoplasty						1						
Cold	2	2		1	2	1			1		1	
Whooping Cough	1				2							
Did not state					1							

It will be noted from the above that 39 of these cases gave pneumonia as a predisposing cause, 21 bronchopneumonia, and 10 influenza There fore, 70 of these 100 cases gave an acute broncho pulmonary disease as a predisposing cause

Seventy six per cent of these patients were referred and had received penicillin aerosol but were allergic to penicillin Tyrothricin aerosol, 500 to 700 micrograms per cc, was used instead by us Only two cases developed allergy to tyrothricin and three people could not use it because they stated it was too irritating to the throat These five cases were treated by an aerosol of 5 per cent solution of sodium sulfathiazole and sodium sulfadiazine combined

Our initial sputum examination by culture showed in a great majority of cases the predominance of gram positive organisms with a few gram-negative organisms However, after a few days of aerosol treatment there was a marked decrease in gram positive organisms and a marked increase in gram negative organisms In 35 cases the initial sputum examination revealed E coli by culture, 13 showed actinomycetes, and two had monilia albicans Only six cases had a co existing sinusitis

Blood studies revealed the initial white blood count ranged from 7,600 to 25,600 the great majority ranging from 12 000 to 18 000 per cubic millimeter

The initial sedimentation rate (Westergren) varied from 18 to 115, the great majority ranging from 28 to 45

Reports as of May 1, 1948, revealed that of the first 42 patients, three were dead one following surgery, one of coronary occlusion, and one of amyloid disease All others, except one chronic alcoholic are doing well The majority continue aerosol treatment at various intervals in the home The same is true of the remaining 58 cases

It was noted that in the 20 to 30 age group at least two had developed the disease in childhood In all other age groups, from the history, the disease had existed from five months to 20 years Study of this group of one hundred cases was begun January, 1945

As of March 1950, a survey of 84 of the above 100 patients was completed The other 16 could not be contacted Those contacted were doing full duty but were continuing aerosol treatments at intervals in the home Many of the cases following inhibitive tests have been changed to bacitracin aureomycin, streptomycin, or Neo-Penil, a derivative of penicillin.

(The above studies were made by the author and Dr Anton Berkman Professor of Biology, Texas Western College of the University of Texas aided by grants from Sharp and Doehme)

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BRONCHIAL FISTULAS

By ANDREW J BANYAI, M D AND J WINTHROP PEABODY, M D

Bronchial fistula as a complication of amebic abscess or echinococcic infestation of the liver is well known Details relative to these two conditions are described in the respective chapters The subject of broncho pleural fistula is covered in the chapter on Diseases of the Pleura

This discussion, therefore, will be limited to the following items

1 Biliary bronchial fistula

2 Bronchial fistula of renal origin

3 Bronchial fistula originating from subdiaphragmatic abscess due to perforation of the stomach, duodenum, small and large bowel

4 Bronchial fistula originating from subdiaphragmatic abscess caused by obscure intraperitoneal or extraperitoneal infection, or which develops after major abdominal operations

5 Esophagobronchial fistula

6 Bronchial fistula communicating with a paravertebral cold abscess

The clinical picture is greatly influenced by the pathogenesis of the fistula In general, it may be brought about by

(a) Infection (entameba histolytica, echinococcus, streptococcus, staphylococcus, Escherichia coli, dysentery bacillus, trepanoma pallidum, tubercle bacillus and other pathogenic micro organisms)

(b) Neoplastic changes

(c) Trauma

With the exception of the last relatively small group, patients give a history of preceding serious disease, such as an abdominal ailment with chills, fever, malaise, anorexia, vomiting, severe pain in the abdomen colicky pain due to gallstone or renal calculus Surgical intervention may have been necessary for the underlying condition Others complain of gradually progressive difficulty in swallowing Rarely, there is definite history or objective evidence of neoplastic or inflammatory disease of the mediastinum or Pott s disease which is responsible for the bronchial fistula With the exception of cases of traumatic origin a considerable interval elapses between the onset of the causative disease and the manifestations of fistula

Symptoms In patients with abdominal disease as the source of the bronchial fistula, malaise and gradually increasing abdominal pain of several months duration may precede respiratory symptoms The latter

ensues with sudden severe pain in the chest, with intense, spasmodic cough and with the expectoration of large quantities of sputum which may have an offensive odor Characteristically, there is no history of serious pulmonary disease directly before this episode From then on, respiratory symptoms may dominate the picture and may entirely overshadow the abdominal phase of the disease There are instances on record where cough and expectoration attributable to such bronchial fistulas persist for several years Frank pulmonary hemorrhage may occur The symptomatology of the disease varies according to the extent and type of coexistent involvement of the lung parenchyma and the pleura There may be concurrent bronchopneumonia, interstitial pneumonitis, lung abscess and bronchiectasis in the lung which is the site of the fistula Also, one may encounter symptoms and signs of plastic pleurisy, pleural adhesions, clear, serofibrinous pleural effusion, encapsulated or free empyema and evidence of pneumothorax on the corresponding side

1 According to Guy and Oleck up to about 1947, there have been only 64 cases of biliary-bronchial fistula recorded in the medical literature Most of these resulted from inflammatory or neoplastic disease of liver or extrahepatic bile ducts Rarely, surgical or nonsurgical trauma was the cause Communication may be established between these lesions and the bronchi either in consequence of abscess formation between the liver and the diaphragm, or adhesions develop between these two structures and the inflammatory process spreads directly to the lung Empyema may be absent at the time when the biliary-bronchial passage first develops In some cases, empyema appears subsequently Patients with biliary bronchial fistula expectorate lemon colored or bright yellow sputum of bitter taste Sometimes, the sputum shows genuine bile color Also, it may contain pus, blood and necrotic liver tissue The daily amount of expectorated bile varies from traces to more than a quart There may be intermittent or steady pain localized in the right hypochondriac area, it radiates toward the shoulder Some of these patients relate that following surgery for cholelithiasis they developed a residual draining biliary fistula through the anterior abdominal wall In spite of this they are able to get along in reasonable comfort When, however, the draining fistula heals over externally, the accumulating bile and inflammatory products may find their way toward the lung and a biliary-bronchial fistula may form within a week or two

Biliary bronchial fistulas of traumatic origin constitute less than

10 per cent of all cases recorded This is surprising at first glance, in view of the numerous combined thoracoabdominal war wounds with simultaneous injury of the liver and lung Guy and Oleck expressed the opinion that this infrequency was due to high mortality caused by hemorrhage or sepsis, or to the absence of pathologic changes sufficiently severe to produce biliary hypertension

2 Renal and perirenal suppuration may lead to bronchial fistula In a review of cases collected from the medical literature as well as from their own experience, Ochsner and Graves noted a 22 per cent incidence of pleural and pulmonary complications Of 85 patients with perirenal abscess, six had perinephrobronchial fistula (7 0 per cent) according to Nesbit and Dick The development of the fistula was associated with abrupt, severe cough and with the evacuation of large amounts of purulent, usually foul sputum Prior to the appearance of complaints referable to the lung, the patients complain of constant or recurrent aches and pains in the costovertebral region, which radiate around the flank to the pelvis In addition, there may be chills, fever, nightsweats loss of weight, weakness and nausea

3 Bronchial fistula which develops as a complication of perforation of an abdominal viscus occurs in inflammatory conditions, ulcers, carcinoma of the various hollow organs of the abdomen, or rarely, it follows trauma and septic peritonitis It has been known to surgeons for a good many years that there exists a so-called subdiaphragmatic drift in the abdominal cavity Infectious material, inflammatory products and pathogenic micro organisms are being carried from any segment of the peritoneal cavity toward the subdiaphragmatic region Consequently, regardless of the site of inflammatory disease or perforation within the abdomen, there is a tendency to accumulation of pathogens and foreign particles underneath the diaphragm This phenomenon is attributable to the normally present negative pressure in the subdiaphragmatic region This has been measured with the aid of an ordinary water manometer by ourselves and by other investigators Negative pressure in this area is a borrowed pressure, that is, it is transmitted from the intrapleural negative pressure The latter is 7 cm of water below the atmospheric pressure on inspiration, and 3 cm of water on expiration The intrapleural negative pressure exerts a suction effect upon the lung and thereby it is capable of holding this organ in apposition to the chest wall in spite of the well known hilusward retractile force of the pulmonary elastic fibers Under physiologic circumstances, the

transmitted negative pressure maintains its suction effect below the diaphragm, although the force of this suction is less than that in the pleural cavity Abscess formation under the diaphragm may take place on either side following infection of other segments of the peritoneal cavity Cases have been reported where, contrary to expectation, perforation of an acutely inflamed appendix was followed by abscess underneath the left hemidiaphragm As a rule, infection spreads readily from the subdiaphragmatic region toward the pleura and the lung but only very rarely in the opposite direction The solution of this apparent paradox lies in the suction force exerted by the normal intrapleural negative pressure The area between the lower surface of the diaphragm and the upper surface of the liver is divided into right and left halves by the falciform ligament Both of these spaces are bisected into large anterior and small posterior sections by the coronary ligament of the liver According to Hertzler the reactive capacity of the peritoneum in the right posterior subdiaphragmatic area is different from that in other sections of the abdomen for the reason that the former region is devoid of subperitoneal connective tissue and vessels Consequently, irritation here produces adhesions much less readily than in other regions

There are only a few recorded cases of *bronchocolic fistula* in the medical literature The first one was reported by Felkl and Michalek The train of events that led to this condition in their patient, a five year old boy, was as follows After lobar pneumonia, the child developed fibrosis of the left lower lobe, with consequent bronchiectasis The latter, in turn, was complicated by encapsulated empyema Subsequently, the empyema perforated into the left subdiaphragmatic region, with resulting abscess formation Following perforation of the subdiaphragmatic abscess into the splenic flexure of the colon, the feces contained free pus Shortly thereafter, infection of the empyema with Escherichia coli took place, bronchopleural fistula developed and free communication was established between the bronchi of the left lung and the colon

Ackermann reported a second case of this unusual condition It was observed in a sixteen-year-old girl who had acute appendicitis complicated by perforation of the appendix and multiple encapsulated abscesses of the peritoneal cavity One of these, localized in the left subdiaphragmatic area was not surgically drained There developed a simultaneous perforation into a bronchus and into the distal segment of the transverse colon

4 Clinical manifestations of bronchial fistulas originating from

obscure intraperitoneal or extraperitoneal infection are similar to those described previously As a rule, bronchial perforation is signalized by sudden severe pain in the chest, with cough and expectoration of considerable, often foul smelling sputum After the evacuation of the pus, the sinus tract may become sealed, with consequent remission in respiratory symptoms Such apparent recovery, however, may be followed by a recrudescence of symptoms due to reopening of the fistula in consequence of the increased pressure of pus which accumulates in the subdiaphragmatic abscess

5 The usual site of esophagobronchial fistula is between the esophagus and one of the main bronchi Either some inflammatory disease malignant tumor or trauma is the inciting cause The symptoms are cough, usually in the form of severe coughing paroxysms on swallowing food, substernal pain dysphagia, vomiting and loss of weight Ingestion of liquids provokes a coughing spell more readily than swallowing solid food Small fistulous tracts may easily permit the passage of liquids from the esophagus to the bronchus while solid food may glide over its esophageal opening without entering the fistula Loss of weight and dehydration are natural consequences of insufficient nutrition on account of the distressing coughing episodes The patient may relate noticing ingested food particles in the sputum

A unique case belonging in this category was reported by Abbott His patient, a 47-year old white physician, was an unfortunate victim of rough fraternity initiation 'ceremonials' Following the forced passage by mouth of a bougie, esophagobronchial fistula developed, with persistent cough which occasionally was productive of small food particles In addition to having had five severe attacks of right lower lobe pneumonia, he was coughing up fluids when he drank them with his head bent forward Clinical studies revealed the presence of fistulous communication between the esophagus and the right main bronchus In spite of competent surgical intervention, the patient died Necropsy findings of significance were

(1) Esophagobronchopleural fistula on the right side
(2) Bronchopleural fistulas on the right side
(3) Thrombosis of the splenic artery
(4) Infarcts in the spleen and left kidney with abscess formation
(5) Bronchopneumonia of the left lower lobe

6 Of all forms of osseous tuberculosis, Pott s disease is the most common There are numerous instances on record where the patient did

not seek medical attention until the tuberculous process in the vertebrae advanced so far that a paravertebral cold abscess developed This, in turn, may lead to mediastinal inflammatory changes and in some instances, to the development of a fistulous passage between the bronchial tract and the cold abscess Coughing paroxysms and expectoration of large amounts of purulent material are typical signs of such an event Constitutional manifestations of tuberculosis are usually present There may be a definite history of exposure to a known source of active tuberculosis In some cases, clinical evidence of active pulmonary tuberculosis is found In others, gross evidence of active tuberculous involvement of the lung is absent, the tuberculous spondylitis having originated from a minute, hidden pulmonary or some extrapulmonary tuberculous focus Bronchial fistula communicating with a paravertebral cold abscess is more likely to be encountered in children but we have seen it occur in adults

A peculiar case belonging to this category was reported by Machado and Diaz in which tuberculosis of the third lumbar vertebra was complicated by a paravertebral cold abscess From this abscess a fistulous tract developed subsequently which extended in cranial as well as caudal directions The upward extension was attributed by the authors to having had the patient on absolute bed rest for a long period of time The downward spread of the abscess resulted in a fluctuating mass in the upper third of the gluteal region On surgical incision of the gluteal cold abscess a bone sequester was removed which was identified as the transverse process of the third lumbar vertebra X ray examination after the injection of iodized oil revealed an irregular fistulous tract traversing along the spine the abdominal and thoracic cavities The fistula connected the gluteal cold abscess with the left main bronchus

Diagnosis An accurate history may offer an important lead in arriving at the correct diagnosis Physical and x ray examinations reveal relevant findings In cases where previous abdominal disease, with or without operation is suspected as the source of bronchial fistula, one may find a palpable mass in one of the upper or lower quadrants, together with local tenderness and muscle rigidity The latter is often absent in children in spite of serious inflammatory process in the abdominal cavity Physical examination over the chest may show signs of pneumonia, bronchitis, bronchiectasis, pleural thickening or pleural effusion On the roentgenogram, one should look for changes indicative of pneumonia, atelectasis, thickened pleura, pleurisy with effusion,

hydropneumothorax and encapsulated pneumothorax. In some instances, there is a radial band like shadow from the basal peripheral part of the lung to the hilum, which signifies pneumonitis along the fistulous tract between the subdiaphragmatic region and one of the main bronchi. The diaphragm is elevated on the side of a subdiaphragmatic abscess and its respiratory excursions are markedly limited or absent. Liver abscess may be recognized from a round defect in the upper contour of the liver shadow. When communication is established between an area of suppuration in the subdiaphragmatic region and the bronchial tract, a horizontal fluid level with air is noted. For better demonstration of this finding it is advisable to take roentgenograms with the patient in the upright and lateral recumbent positions, with the diseased side uppermost. Serial films are of value in diagnosis as well as in following the course of the disease. Perforation of the stomach or the intestine is associated directly after its development with the presence of air underneath the diaphragm. For its demonstration, it is well to take roentgenograms in the upright and lateral recumbent positions. Diagnostic pneumoperitoneum is a useful method and consists of the intraperitoneal injection of from 500 to 1,000 cc of air. It is a simple and safe procedure. Local anesthesia is done three fingers breadth below and at the same distance to the right or left of the umbilicus. One should avoid areas near the site of the primary abdominal disease. A 19 gage needle, connected with a rubber tube to the manometer of a pneumothorax apparatus, is gently forced through the abdominal wall. A three way stopcock attached to the needle makes the procedure easier in that it permits attempts at aspiration through the needle without removal of the rubber tube. When the needle penetrates through the abdominal wall slowly, the risk of puncturing the stomach or intestine is practically nil. One should rely on the sense of touch as to when the point of the needle reaches the peritoneal cavity. It is mandatory to attempt aspiration through the needle before injecting air so that one is sure that the point of the needle is not in a blood vessel. In this manner, the danger of air embolism is avoided. In a case of subdiaphragmatic abscess, after diagnostic pneumoperitoneum has been induced, the air injected does not reach the subdiaphragmatic space on the diseased side.

Instillation of iodized oil is an invaluable means for the roentgenologic demonstration of bronchial fistulas. It can be done with the aid of a bronchoscope, by injecting the contrast medium in the sub-

diaphragmatic abscess, or both Iodized oil injected into a subdiaphragmatic abscess is bound to cause a sudden coughing spell when it enters the bronchi Roentgenograms taken at right angles and with the patient in the oblique position will aid in the exact localization of the fistula

When methylene blue or gentian violet is injected into a subdiaphragmatic abscess with a bronchial fistula, dye is expectorated during the coughing spell that follows the injection Esophagobronchial fistulas are readily demonstrable with the injection of one of these dyes either through a bronchoscope or an esophagoscope directly into the fistulous tract

In addition to the aforementioned physical and x ray findings and to symptoms referable to the chest, such as cough, expectoration and dyspnea, constitutional symptoms may be noted These include chills, fever, sweating, malaise, loss of appetite and loss of weight In cases of biliary bronchial fistula, bile is detectable in the sputum with the Gmelin test Clubbing of the fingers may be observed Thoracocentesis may reveal serofibrinous or purulent pleural effusion The presence and degree of leucocytosis is predicated upon the type and extent of the causative disease and the severity of pleuropulmonary complications

Differential Diagnosis From the clinical standpoint in general, and from the roentgenologic standpoint in particular, the following conditions should be ruled out lung abscess, bronchopleural fistula, congenital cystic disease of the lung with multiple or solitary cyst, pulmonary echinococcus cyst, teratoma of the lung, tuberculosis with large cavity and massive expectoration, bronchiectasis, mediastinal abscess perforating into a bronchus, mediastinal cyst, diaphragmatic hernia, eventration, pneumonia, atelectasis, massive fibrosis, benign or malignant tumors, pulmonary amyloidosis, syphilis, sarcoidosis and pleurisy with effusion

Prognosis When the origin of bronchial fistula is not due to malignant neoplasm, spontaneous healing may take place after the evacuation of the abscess that led to the formation of the fistula On the other hand, if the underlying disease is not given proper attention, serious pleural or pulmonary complications may arise, such as empyema, pneumonia or lung abscess which directly or indirectly may cause the patient s death

Treatment Healing of bronchial fistulas is promptly effected by adequate surgical drainage of the subdiaphragmatic abscess from which they originate Specific chemotherapeutic measures, antibiotics and surgical intervention should be resorted to for coping with concurrent

affections of the liver, gastrointestinal and urinary tracts Guy and Oleck recommend the transthoracic approach for the treatment of biliary bronchial fistula This method permits freeing the lung from the fistulous opening in the diaphragm, exploration and drainage of the pleural cavity, enlargement of the fistulous opening in the diaphragm, exploration of the subdiaphragmatic space, drainage and packing of the hepatic abscess They emphasize that the advantages of this operation far outweigh the potential danger of opening up uninfected areas of the pleura, producing open pneumothorax and consequent pulmonary collapse Closure of the esophagobronchial fistula may be attained by the introduction of sodium hydroxide crystals through an esophagoscope directly into the fistula In other instances, direct surgical repair is indicated Maintaining satisfactory nutritional status of the patient is of paramount importance Feeding through a nasal tube is expedient for this purpose In other instances, early gastrostomy may be required Abbott suggested jejunostomy as a measure preferable to gastrostomy on account of the frequency with which coughing paroxysms are provoked on each gastrostomy feeding In some cases, pulmonary resection and thoracoplasty may be required for the closure of an esophagobronchial fistula

Kidd and Christopherson reported a rare case having both bronchoesophageal fistula and broncholithiasis Diagnosis of bronchlithiasis was established by expectoration of calculi but the fistula was not revealed by bronchograms Recovery followed pneumonectomy

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BRONCHOPULMONARY LITHIASIS

By Andrew L Banyai M D and J Winthrop Peabody, M D

In patients with chronic pulmonary disease, bronchopulmonary lithiasis is more common than generally appreciated The number of pertinent records in the medical literature does not reflect the true incidence of this condition First, because in the overwhelming majority of instances the patient does not seek medical attention and therefore, he is not scrutinized roentgenologically Secondly, even when the condition is recognized, as in innumerable cases of healed primary or reinfection tuberculosis, the occurrence of disturbing clinical symptoms is comparatively rare

Chemically, lung stones consist of about 85 to 90 per cent calcium phosphate and 10 to 15 per cent calcium carbonate This is the same composition as that of normal bone In addition, there may be traces *of carbon, iron, magnesium oxalate, silica and organic matter, such as* cholesterol, fat, mucus Pneumoliths and broncholiths may represent calcification or ossification with haversian canals Their color is grayish or brownish white, infrequently, yellow or black They present a smooth or rough, spiked surface and irregular shape, with great variations in size, from gravel like appearance to more than 100 gm in weight Their consistency is hard or putty like Pulmonary stones may be solitary or multiple, localized in a limited area or widely distributed in both lungs

From the standpoint of topography and origin, pneumoliths and broncholiths are classified as follows

1 Parenchymal and interstitial
2 Bronchial A) *Endobronchial B) Intramural*
3 Lymph node A) Hilar B) Peribronchial
4 Pleural
5 Aspirated from the oral cavity or from the upper air passages rhinoliths, calculi from the tonsils, salivary glands, bone fragments following operations, dental concretions

Calcification which develops in the lymph nodes, the lung or pleura usually follows tissue necrosis severe inflammation or hemorrhage Wells advanced the concept that the comparatively high incidence of concretions in the lung is attributable to an increase in the pH of the tissue in this organ, due to loss of carbon dioxide Presumably, decrease in the *acidity predisposes to the deposition of calcium salts*

A case of diffuse intra alveolar pulmonary microlithiasis of idiopathic

origin was reported by Puhr in 1933 Mariani and his associates recorded a similar instance On post mortem examination they observed that the air content of the lung was very slight and that there were in the lung widely distributed small hard nodules of concentric layers of calcium salts, with a scanty cellular accumulation in the center The dominant symptoms were dyspnea and cyanosis X ray examination revealed a veil-like shadow over the lung fields, with numerous small, round, dense opacities measuring from 2 to 4 millimeters in diameter throughout both lungs

As to the pathomechanics of pneumoliths and broncholiths, the following categories are to be considered

Incentive Cause	Types	
Necrosis and Severe Inflammation	Tuberculosis	Primary Reinfection Miliary
	Fungus Infection	Actinomycosis Aspergillosis Blastomycosis Coccidioidomycosis Histoplasmosis Moniliasis
	Bronchopneumonia Parasitic Infestation Abscess Bronchiectasis Pneumoconiosis Neoplasms (Sarcoma, Hamartoma, Teratoma) Cysts	
Hemorrhage	Mitral Disease Renal Rickets Infarction Trauma	
Senile	Calcification of Bronchial Cartilages Perivascular Calcification	
Agnogenic	Scleroderma Thibierge Weissenbach Syndrome Multiple Myeloma Multiple Carcinomatous Metastasis to Bones Hypervitaminosis D Hyperparathyroidism Diffuse Intra alveolar Microlithiasis Diffuse Interalveolar Microlithiasis	

Most of the calcarious concretions in the lymph nodes, lung and pleura remain inert at the site of their development indefinitely Symp toms and signs appear when they migrate into the bronchial lumen irritate surrounding tissues or erode adjacent blood vessels In such instances, the most common symptom is cough First, it is unproductive *and may be persistent or paroxysmal In association with the latter, the* patient may expectorate broncholiths of various sizes Boerhaave, in 1744 observed a patient who expectorated 400 lung stones Immediate and dramatic relief from all symptoms may follow the expectoration of a broncholith or broncholiths When bronchial occlusion is brought about by a broncholith, bronchial infection, bronchiectasis, atelectasis, or bronchopneumonia may develop In such an event, the patient presents himself with symptoms and signs characteristic of these conditions Usually, there is pronounced increase in his cough, also, there is ample sputum, purulent or foul Moreover, one may find evidence of compli cating pleural effusion which may be serous or purulent Other possible complications of broncholiths are spontaneous pneumothorax, pneumo-mediastinum and lung abscess

Pulmonary hemorrhage is a common manifestation of migrating broncholiths The sputum may be blood streaked or the patient com plains of a brisk, massive hemorrhage Fatal pulmonary hemorrhage *has also been reported*

During the slow migration of a broncholith, the patient may have dull pain in the parasternal or interscapular region Sudden perforation of a stone into a bronchus is accompanied by sharp, tearing pain

Partial bronchial obstruction is likely to be associated with dyspnea and wheezing which may closely simulate bronchial asthma

Constitutional symptoms are found in patients who develop a secondary infection distal to the occluding stone These include chills, fever, malaise and weight loss

An accurate history is of utmost importance in establishing the diagnosis In all cases of obscure hemorrhage from the lungs it is well *to inquire specifically about the expectoration of calculi* The authors have a good sized collection of pneumoliths brought in by patients as suspected corpus delicti

Physical examination of the chest is noncontributory to diagnosis unless there are significant complications

X ray examination of the lung by fluoroscopy, simple roentgeno grams, heavy penetration films and tomograms is of great value One

can readily visualize and localize the calciferous focus in this manner There is no favorite localization of these structures In search for solitary stones, it is well thoroughly to scrutinize the hilar region, preferably with the aid of oblique roentgenograms Bronchogram with iodized oil is useful in demonstrating bronchial stenosis, bronchiectasis or occlusion Also, roentgenograms reveal the presence of complications, such as atelectasis, bronchopneumonia, abscess, pneumothorax, pneumomediastinum and pleural effusion

On bronchoscopic examination, one may see the calculus within the bronchial lumen or lodged in the bronchial wall In other instances stenosis, erosion, ulceration or granulation is noted at the site of the stone

Inasmuch as symptoms and signs caused by migrating broncholiths may be encountered in a number of other conditions, extreme care must be exercized in the differential diagnosis When pulmonary hemorrhage is the presenting symptom, the following diseases should be ruled out

Active inflammatory diseases of bacterial, viral, rickettsial, parasitic or chemical origin
Tumors, benign or malignant
Aspirated foreign bodies
Infarction
Mitral stenosis
Vascular anomalies of the bronchial mucosa (varicosities)
Arteriovenous fistula
Hereditary hemorrhagic teleangiectasia
Aneurysm
Blood dyscrasias
Collagen diseases including periarteritis nodosa
Pneumoconiosis
Vitamin deficiency
Hypertension

In connection with other symptoms, such as wheezing, pain in the chest, dyspnea, cough and expectoration one should take into consideration the possibility of bronchial asthma, tumors of the lung, bronchiectasis, lung abscess chronic pneumonitis, bronchial occlusion of extrinsic origin (mediastinal tumors, aneurysms enlarged lymph nodes), whooping cough chronic bronchitis angina pectoris and congestive heart failure It is mandatory to carry out a thorough and

competent search for pathogenic micro-organisms and malignant cells It is well to remember that expectoration of broncholiths does not exclude active pulmonary tuberculosis or a coexistent lung tumor

Prognosis is greatly influenced by the presence or absence of one of the aforementioned complications and the severity of the mechanical damage done by the migrating broncholith Reference has been made to the possibility of fatal pulmonary hemorrhage. On the other hand, in some instances, expectoration of a broncholith is followed by complete and permanent relief from symptoms

Treatment There are instances where bronchoscopic removal of a calculus gives excellent results Careful manipulation is necessary during this intervention so as to avoid further injury to the damaged bronchial structures and adjacent blood vessels and obviate increase in the hemorrhage When bronchoscopic removal of a broncholith is not feasible, segmentectomy or lobectomy may be indicated Successful removal of broncholiths in 10 cases by segmental resection, lobectomy or pneumonectomy was recently reported by Schmidt and his co-workers Secondary infections are attended to in the manner described in the corresponding sections Anemia is to be corrected In massive hemorrhage, blood transfusion is called for

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Chapter III

PULMONARY ABSCESS

By J A Myers M D

GENERAL CONSIDERATION

PULMONARY abscess is the term used to designate local suppuration involving lung tissue In size abscesses vary from a few millimeters to ten or more centimeters in diameter They may be single or multiple and involve one or both lungs The term simple abscess has been applied (Overholt *et al*) to one of short duration (six weeks or less) with single or multilocular cavitation without secondary bronchiectasis while complicated abscess consists of multiple, isolated daughter lesions located, in a zone of pneumonitis which are not connected with the primary cavity They occur in all parts of the lungs with a preponderence in the lower portions Pulmonary abscesses develop at all ages of life with approximately 50 per cent between 20 and 40 years They occur about twice as frequently in males as in females

Pulmonary abscesses are believed to be caused by infected emboli which lodge in the lungs and micro organisms which are aspirated from the mouth and throat When substances such as barium, iodized oil, bacteria and stain were placed in the mouths of anaesthetized animals by Lemon aspiration occurred regardless of the depth of anaesthesia when the animals were on planes inclined at various degrees but with the head elevated above the body Struggling, swallowing or vomiting under light anaesthesia increased the amount aspirated As the downward inclination was increased aspiration decreased and was completely prevented when the Trendelenberg position was reached Among the animals which aspirated these materials Lemon later found in their lung tissues bacteria which he had placed in their mouths as well as organisms which frequent the mouth and throat Therefore it is likely that during surgical operations requiring general anaesthesia

there is great danger of aspiration of pathogenic micro organisms unless care is given to the position of the body When upper respiratory infections are present the hazard is increased If adequate precautions are not taken, pulmonary abscesses occur with considerable frequency following operations on the mouth, nose and throat such as extraction of teeth and tonsillectomy

Bronchial obstruction caused by tumors, etc, may lead to abscess in the lung Occasionally they follow pneumonia, due, in part, to mucus plugs which obstruct bronchial ramifications Sometimes pulmonary infarcts break down so as to form abscesses Foreign bodies in the bronchi may also result in abscess formation Such bodies may be aspirated in the usual way and are most frequently found in the lower lobes, especially the right This probably is due to the fact that the right bronchus is the more direct continuation of the trachea Vinson called attention to calcific deposits which find their way through the walls of bronchi and are aspirated peripherally so as to result in abscess formation



Fig 1 This woman of 33 years developed pulmonary abscess in the right lung following appendectomy in 1937 Her respiratory symptoms were severe until she expectorated a large amount of fetid pus She made a complete recovery with no aid except ordinary medical care (From Myers J A and McKinlay C H *The Chest and The Heart* Springfield Illinois Charles C Thomas Publisher 1948)

Abscesses enlarge by direct extension or by spread of the infected material through the surrounding bronchi Pulmonary gangrene is considered by some physicians as an independent disease entity They regard those conditions caused by fusiform bacilli and spirochetes with fetid sputum, as gangrene, while those infected with other organisms are considered abscesses It appears however, that abscess and gangrene

ely represent manifestations of the same disease For example, if a e amount of abscess material is carried to other parts of the lung, grenous pneumonia may result Extremely acute abscesses sometimes me gangrenous with a rapid, fatal course They may result from olism or thrombosis of pulmonary vessels

Diagnosis

TORY

Recent surgery, particularly of the mouth, nose, or throat, or an ck of pneumonia, may be significant Pulmonary infarcts may lop especially following operations on the pelvis which sometimes to abscess formation History of a recent period of unconsciousness n any cause, of choking while swallowing food or an attack of cough wing aspiration of some other object often is significant from the dpoint of foreign body abscess In some cases no history of pre- ting conditions such as those mentioned above is obtainable This is icularly true of foreign body abscesses in children

PTOMS

The first manifestation of pulmonary abscess may be a chill followed ever similar to that of pneumonia In the early stage of the disease gh and expectoration usually are slight or entirely absent As the



2 This girl of 12 years first examined in 1929 use of possible exposure iberculosis Her chest was r and remained so until ch 1931 when she re ed following a pulmonary orrhage In January 1931 illectomy was performed er general anesthesia and had expectorated consid le fetid sputum during two weeks prior to the monary hemorrhage A e, homogeneous shadow seen on the right side nonary abscess was diag d and she was admitted a hospital where a needle was introduced in an attempt to aspirate from the ess cavity She developed mixed infection empyema and extension of the abscess ... ding errors were (1) Failure to prevent as ile under general anesthesia during tonsillec abscess (From Myers J A and McKinlay gfield Illinois Charles C Thomas Publisher 3)

there is great danger of aspiration of pathogenic micro organisms unless care is given to the position of the body When upper respiratory infections are present the hazard is increased If adequate precautions are not taken pulmonary abscesses occur with considerable frequency following operations on the mouth, nose and throat such as extraction of teeth and tonsillectomy

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Abscesses enlarge by direct exten material through the surroundin considered by some physicians a regard those conditions caused b fetid sputum as gangrene A are considered abscesses It ap

elicited when the area of disease is large and near the surface These sometimes are consonating if cavities are only partially filled

From the surface of the body one often sees *clubbing of the fingers and toes* which may appear within a few weeks after onset of the abscess *Hypertrophic pulmonary osteoarthropathy* develops in some cases This consists of new bone formation in the shafts and periosteum of the



Fig 3 In December 1935 this girl of 12 years had a diagnosis of influenza. Cough persisted and she reported to a physician in August 1946 Evidence of extensive disease was found in the right lung A few days later she suddenly expectorated a large amount of fetid pus She was treated by strict bed rest and usual medication of that time In October she had a profuse pulmonary hemorrhage Large numbers of spirochetes and fusiform bacilli were recovered from her sputum Small doses of neosavarsan were administered and all evidence of the abcess disappeared within a few weeks (From Myers J A and McKinlay C H *The Chest and The Heart* Springfield Illinois Charles C Thomas Publisher 1948)

phalanges and metacarpals as well as enlargement of the soft tissues in these areas The distal ends of the radius and ulna may be involved and in some cases these changes extend to other bones of the body This condition may also accompany other diseases of the heart and lungs Its cause is not well known Some physicians believe it is the result of toxins from the area of disease, while others think it is due to anoxemia These conditions may completely disappear when the abscess is brought under control at an early stage

Movements of the chest wall on respiration are often limited on the affected side, and the phrenic wave sign is decreased or absent In abscesses with acute severe onset, the patient appears seriously ill

Roentgen inspection, both with fluoroscope and the film, is a valuable phase of the examination for determining the location and extent of gross disease. In this manner one may locate lesions before conventional

condition progresses, cough becomes severe. The sudden expectoration of a large quantity of fetid sputum, a half cupful or more, is not uncommon when an abscess ruptures into a ramification of a bronchus. Pleural pain is a common symptom. Abscesses following operations and aspirations from the mouth and throat usually have a sudden and severe onset with profuse sweating and prostration. On the other hand, abscesses which occur with slowly developing obstructions may have a more gradual onset with less severe initial symptoms, such as general aching of the body and malaise. Expectoration of blood varying in amount from streaks in the sputum to fatal hemorrhage, occurs in pulmonary abscess. Symptoms of multiple abscesses due to emboli from a suppurative condition elsewhere in the body may be masked by those of the other disease. However, one should always keep in mind this possible complication and if symptoms such as chest pain, cough, and expectoration appear, multiple abscesses should be suspected. Symptoms are not pathognomonic since all of them except the sudden expectoration of a large amount of fetid purulent material are caused by other conditions, and even this also occurs in empyema.

EXAMINATION

Over small deeply located abscesses, no abnormal sign is elicited by palpation. On the other hand, if they are large with extensive inflammation of the adjacent lung tissue, tactile fremitus may be increased. When pleural exudates are present tactile fremitus may be decreased or absent. In cases of long standing, decrease in movements of the chest wall on respiration is palpable. Rigidity of chest muscles which often is palpated is caused by the reflex protective mechanism. When abscesses are of long standing, however, the muscles atrophy.

If the abscess is small, the percussion note is normal but when it is large and near the surface a dull to a flat note is elicited. Over large empty cavities near the surface of the lung a tympanitic note may be heard.

The breath sounds are normal if the area of disease is small but as it becomes larger, bronchial breathing is often heard. Over large cavities near the surface which are partially or completely empty, amphoric breath sounds are usually elicited. Spoken and whispered voice sounds depend upon the extent of disease and its location. They are bronchial in character over the areas where bronchial breathing is heard, and if large, empty cavities are present, they are amphoric. Rales are usually

elicited when the area of disease is large and near the surface These sometimes are consonating if cavities are only partially filled

From the surface of the body one often sees clubbing of the fingers and toes which may appear within a few weeks after onset of the abscess *Hypertrophic pulmonary osteoarthropathy* develops in some cases This consists of new bone formation in the shafts and periosteum of the



Fig 3 In December 1935 this girl of 12 years had a diagnosis of influenza. Cough persisted and she reported to a physician in August 1936 Evidence of extensive disease was found in the right lung A few days later she suddenly expectorated a large amount of fetid pus She was treated by strict bed rest and usual medication of that time In October she had a profuse pulmonary hemorrhage Large numbers of spirochetes and fusiform bacilli were recovered from her sputum Small doses of neosalvarsan were administered and all evidence of the abscess disappeared within a few weeks. (From Myers J A and McKinlay C H *The Chest and The Heart* Springfield Illinois Charles C Thomas Publisher 1948)

phalanges and metacarpals as well as enlargement of the soft tissues in these areas The distal ends of the radius and ulna may be involved and in some cases these changes extend to other bones of the body This condition may also accompany other diseases of the heart and lungs Its cause is not well known Some physicians believe it is the result of toxins from the area of disease, while others think it is due to anoxemia These conditions may completely disappear when the abscess is brought under control at an early stage

Movements of the chest wall on respiration are often limited on the affected side, and the phrenic wave sign is decreased or absent In abscesses with acute severe onset, the patient appears seriously ill

Roentgen inspection both with fluoroscope and the film, is a valuable phase of the examination for determining the location and extent of gross disease. In this manner one may locate lesions before conventional

physical signs can be elicited Some abscesses, on the other hand, are not located by x-ray inspection as they are obscured from view by shadows of the heart, diaphragm, etc Unfortunately, abscesses do not cast characteristic shadows However, shadows often lead one to strongly suspect abscess but the cavitations, consolidations, infiltrations, etc, evidenced by x ray shadows are no different from those produced by a number of other diseases Location of the lesion which casts the x ray

Fig 4

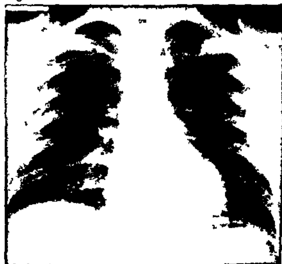


Fig 5



Figs 4 and 5 This man of 23 years was admitted to a hospital on January 18 1944, with a discharging sinus on the left side of the neck abscess right lung (Fig 4) brain abscess due to Staphylococcus On January 20 he received 150 000 units of penicillin intravaneously He also received 15 000 units of penicillin intramuscularly every three hours On January 31 the dose was changed to 10 000 units on February 11 to 5 000 units and on February 17 to 2 500 units every three hours An intraspinal administration of 10 000 units was given on January 21 Penicillin was discontinued on February 22 Although pleural fluid was present on both sides for a while, all evidence of fluid and pulmonary abscess rapidly decreased and he was ambulatory on discharge from the hospital on February 29, 1944 There has since been no evidence of pulmonary abscess (Fig 5) and no symptom referable to brain abscess (Courtesy Dr C J Watson) (From Myers, J A and McKinlay C H *The Chest and The Heart* Springfield Illinois, Charles C Thomas Publisher 1948)

Fig 6



Figs 6 and 7 In November, 1939 this man of 34 years had pneuomia with convalescence extending over several weeks In March 1940, he had an acute flare-up Over the next few months he improved but continued to suffer from malaise and weakness In April 1944 he developed persistent cough and expectorated fetid blood tinged sputum His physician suspected tuberculosis and sent him to a sanatorium where pulmonary abscess was diagnosed Frequent hemorrhages occurred during May 1944 The largest daily quantity of blood expectorated was 14 ounces Did not respond to usual treatment (Fig 6) Right pneumonectomy was performed in November, 1944 Empyema developed and thoracoplasty was performed in December, 1944 (surgery by Dr O H Wangensteen) Now in reasonably good health (Fig 7)

shadow is not a safe criterion Although many abscesses appear in the lower half of the lung they may, and often do, appear in the upper half

One may or may not be helped by bronchograms even when cavitation exists If completely filled with pus, even large cavities present no fluid level, their outlines cannot be seen so their presence is not detected



Fig 7

on the x ray film If iodized oil is ... such cases it fail
enter the cavity Therefore, before atter ... inspection of
chest when cavity from any cause is p ... should be
to have them evacuated th ... igh postu ... etc Even if
are only partially emp ... level
usually see the outline ... wall ... ique oil
enter and being heav ... it ... most
part of the cavity, ... which
is evacuated after w

to size and location of cavities In differentiating between bronchiectasis and abscess, the bronchogram also is helpful The roentgenogram is of great value in observing the progress of abscesses It often reveals decrease or extension of areas of disease and changes in size of cavities before other phases of examination are of any avail Therefore the x ray should be used freely, not only as an aid in the diagnosis of abscess, but also in observing extension or retrogression

Bronchoscopic inspection should always be done when the attending physician is in doubt either as to the presence of abscess or its etiology The bronchoscopist aids greatly in locating an abscess by determining from which bronchus or ramification pus exudes A decade ago bronchoscopy was looked upon as a drastic and major procedure However, bronchoscopists have become so skillful that their procedures now are usually without danger and cause much less discomfort The bronchoscopist s inspection of parts of the involved area may reveal evidence of obstruction When due to a foreign body, it may be removed If the obstruction is due to some other cause a piece of the tissue is procured for microscopic inspection Malignancy is often first detected in this manner Pus may be aspirated for bacteriological and cytological examinations and iodized oil introduced so that good bronchograms are obtainable Abscesses are often first diagnosed as pneumonia because of the similarity of the symptoms Atelectasis due to bronchial obstruction casts a dense homogenous shadow which may not differ significantly from that cast by pneumonia If the broncoscopist is called as soon as abscess is suspected, the removal of obstruction in some cases will establish free drainage and thus control the atelectasis and markedly reduce the potentialities of the abscess Coryllos found that even if the condition is finally diagnosed as lobar pneumonia no harm has been done

The last court of appeal with reference to etiology in many cases of pulmonary abscess is microscopic inspection Only through this phase of the examination can one determine with accuracy the presence of cancer in tissue removed by the bronchoscopist Papanicolaou, Farber and others have been able to demonstrate neoplastic cells in the sputum in a remarkably high percentage of persons with primary carcinoma of the lungs Smears made from sputum or bronchoscopic aspirations may reveal the presence of organisms such as spirochetes, fusiform bacilli, Friedlander s bacilli streptococci, diphtheroid and fungi Bacillus coli and gas bacillus have occasionally been found Pulmonary abscesses may occur in tularemia and amebiasis Therefore these diseases should always

be kept in mind when the physician is seeking the etiology of pulmonary abscess

Some of the more common conditions which must be considered in the differential diagnosis are empyema with rupture into a bronchus, bronchiectasis, cystic disease, and pulmonary tuberculosis

Treatment

Inasmuch as from 25 to 30 per cent of the patients recover from simple abscess spontaneously or with ordinary medical care, the physician should use extreme caution in evaluating any form of treat ment Unless definitely more than 25 to 30 per cent recover, the treatment administered has accomplished no more than would have been done by nature If this fact is constantly kept in mind therapeutic fads will be avoided On the other hand, the fact that 25 to 30 per cent do come under control spontaneously or with ordinary medical care must not mislead the physician into procrastination The individual patient is more likely to belong to the 70 to 75 per cent whose disease requires special therapy and surgical procedures if good results are to be accomplished

Ten to 14 days usually pass after the onset of symptoms before simple abscesses rupture spontaneously into bronchi Strict bed rest is indicated during this time and immediately after, with mild sedatives as necessary to insure relief from nervousness, cough and pain The air of the patient s room is best when maintained at a temperature of approximately 68 to 70 degrees with a relative humidity of about 40 per cent, the air in slow circulation and as free from contamination as possible

Nourishing but light food with adequate number of calories and vitamins is necessary Stimulation of the appetite and administration of drugs to control secondary anemia are important Blood transfusions may be indicated Oxygen should be given on the appearance of cyanosis While the abscess is acute, one should guard against paralytic ileus

No attempt should be made to aspirate a pulmonary abscess by introducing a needle through the chest wall either for diagnostic or therapeutic reasons The needle may cause rupture into the free pleural space or this space may be contaminated as the needle is withdrawn with resulting mixed infection empyema Pneumothorax may also be produced by leakage of air through the needle tract from the lung into

the pleural cavity Manipulation of the needle can cause hemorrhage, air embolism or spread of the pulmonary disease Moreover, it is impossible to adequately drain an abscess through a needle as its contents consist of necrotic tissue, clots and thick pus

When rupture has occurred and while patients are cyanotic, have high fever, rapid pulse, low vital capacity and marked prostration attempts at postural drainage are dangerous They may even prove fatal In the absence of severe symptoms however, postural drainage two or three times a day is a distinct aid If this is not adequate bronchoscopic aspiration may be necessary The bronchoscopist often aids materially by establishing free drainage through a bronchus by dilation of strictures, removal of foreign bodies and obstructing granulation tissue, and by aspirating the contents of the cavity Cavities should be drained as thoroughly as possible by one method or another

When the sputum is fetid creosote vapor containing inhalations are helpful Creosote carbonate is sometimes administered by mouth beginning with 6 drops in hot water and increasing to 15 drops three times a day Frequent use of mouth washes also aid in controlling the fetid odor

When pulmonary abscess is caused by an organism for which there is some specific treatment, this should be administered at once For example, when endamoeba histolytica is the cause emetine hydrochloride (one grain subcutaneously for eight days) should be administered Nearly all patients recover on this treatment, as shown by Ochsner *et al* When fusiform bacilli and spirochetes are present and even in some cases in whom these organisms are not recovered, the arsenicals often are of value An initial dose for adults of 0 15 gram of neosalvarsan repeated every three or four hours until there is clinical improvement and the sputum becomes negative for the organisms has been found efficacious by Spector and others In some cases the dose is increased to 0 3 gram while in others better results are obtained when it is decreased to 0 1 or even to 0 05 gram The treatment should be started early in the course of the disease if antibiotics fail Abscesses due to Pasteurella tularensis may respond well to penicillin and streptomycin When Brucella organisms cause pulmonary abscess it is treated as is brucellosis in general Spink has found streptomycin and sulfadiazine of value in this disease

Penicillin in large doses should be administered intramuscularly as soon as possible after the diagnosis of abscess is made, particularly if

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located One stage external drainage is regarded as feasible, practical and safe

Such procedures as interruption of the phrenic nerve, artificial pneumothorax and extra pleural thoracoplasty are usually of no avail Artificial pneumothorax may even be responsible for the development of empyema

When the disease becomes chronic and is confined to a single lobe lobectomy may result in complete cure of the patient By segmental resection the surgeon is often able to remove only the involved part of a lobe If more than one lobe is involved and the disease is unilateral, total pneumonectomy may be the patient s only hope

INOPERABLE CASES

Chronic cases who will not submit to surgical procedures or in whom they are not indicated may have iodized oil introduced so as to fill the cavity as completely as possible This has no germicidal effect, but being heavier than the cavity contents, it facilitates removal of the infected material Autogenous vaccines have been reported to be helpful in some cases Intravenous administration of sodium benzoate, 10 cubic centimeters of a 20 per cent solution twice daily for three to five days, has been reported of value in some cases If it causes immediate symptoms, such as abdominal pain and dizziness, relief is obtained by the administration of a few drops of tincture of opium or belladonna

The sulfonamides have been used extensively, both in acute and chronic abscesses but without brilliant results, although nebulized sulfonamide solutions have been reported to relieve symptoms Penicillin nebulized daily for a few weeks may be helpful in destroying gram positive organisms If gram negative bacteria are abundant in the sputum and symptoms are still present, streptomycin dissolved in physiologic saline solution may be nebulized daily One may also combine penicillin and streptomycin in 20 to 30 cubic centimeters of saline for daily nebulization Supraglottic instillations of 100 000 units of penicillin and 500 000 units of streptomycin in one administration each day may be useful Large doses of penicillin may also be used intramuscularly at the same time for a brief period Such medication does not cure pulmonary abscesses Symptoms return sometime after the drugs are discontinued However, considerable temporary rel ef may be afforded from time to time

X ray therapy and diathermy have been used considerably without spectacular results Moreover, the x ray is capable of doing harm

gram positive bacteria predominate. Some workers have reported better results when penicillin and sulfadiazine are used together than when either is administered alone Intratracheal administrations of penicillin have been used with apparent good results Aerosolized penicillin has been used considerably, but its popularity is waning because of the increased incidence of sensitivity induced by contact of this drug with mucous membranes Moreover, it does not reach any higher concentration in deep suppurative foci than when administered parenterally Streptomycin given intramuscularly is of value when gram negative bacteria predominate Simultaneous administration of penicillin and streptomycin is indicated when large numbers of both gram positive and gram negative organisms are present Among the newer drugs, aureomycin and terramycin may be used to advantage in some cases

Rarely should the above methods of treatment be continued more than two or three weeks unless satisfactory control of the disease is being accomplished By that time, if marked improvement has not occurred as manifested by reduction of symptoms and decrease of x ray shadows external surgical drainage is indicated before chronic infection results in bronchial damage and the formation of parenchymal fibrous tissue Introduction of penicillin directly into the abscess cavity is often helpful following external surgical drainage

Surgical consultation should be arranged in every case of pulmonary abscess as soon as the disease is detected The surgeon often is able to make suggestions or actually carry out certain procedures that markedly hasten the patient s recovery if he is called sufficiently early Failure to consult with the surgeon may seriously jeopardize the patient s future, as complications often develop, such as bronchiectasis, thick walled cavities, empyema, metastatic abscesses, septic pneumonia profuse and even fatal hemorrhages, air embolus, amyloidosis arthritis, damage of heart muscle, secondary anemia and general debility If some of these complications develop surgery is rendered difficult, if not impossible Overholt *et al* consider that cure of an abscess depends on adequate oxygenation of the cavity and the removal of its contents—necrotic lung tissue and debris They are of the opinion that conservative measures including supportive therapy, drugs, postural drainage and bronchoscopic aspirations do not suffice because of the small calibre of the draining bronchi Pulmonary abscess therefore, is considered a surgical disease and they believe external drainage should be instituted without delay as soon as the diagnosis is established and the disease is accurately

located One stage external drainage is regarded as feasible, practical and safe

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Prognosis

Since 25 to 30 per cent of the cases with simple abscesses heal spontaneously, the prognosis is good for this group However, for the remaining 70 to 75 per cent the prognosis must be guarded The poor outlook in many of these cases in the past has been because treatment was too conservative and the surgeon was not called sufficiently early Recovery rarely occurs spontaneously if the disease is allowed to persist more than a few weeks Therefore, surgical consultation as soon as the diagnosis is made may markedly improve the prognosis in a high percentage of those in whom it would otherwise be poor Among 205 cases reported by Brunn, 133 were treated medically at home of whom 31 per cent improved, and 35 per cent died The remaining 34 per cent were not referred to surgeons until an average of 460 days after the disease was first diagnosed Of the remaining patients in this group, 72 were treated surgically, of whom 56 per cent improved Even in these improved cases surgery was not instituted until 415 days after symptoms first appeared Forty-four per cent of these 72 patients died, but surgery was not begun until 516 days after the disease appeared

If pulmonary abscess is extensive or complicated from the beginning, symptoms are severe or gangrene is present, the prognosis is poor even when the best known treatment is administered Bilateral multiple pulmonary abscesses often are fatal Empyema and other complications cloud the prognosis

Prevention

The incidence of pulmonary abscess has markedly decreased during the past 20 years The preventive measures practiced apparently have had much to do with this situation, and still more should be accomplished through them The following preventive measures are important

Oral hygiene has most likely played a large role Children develop pulmonary abscess and gangrene much less frequently than adults Probably this is partially because it is not until adulthood that the mouth becomes extensively contaminated with organisms capable of producing abscess through such conditions as pyorrhea and other foci of infection A greater number of abscesses appear in the lungs of men than in those of women, which may be because men have usually practiced much poorer oral hygiene than women The campaign of the

dentists for better oral hygiene has probably borne fruit in the reduction of the incidence of pulmonary abscess

Preparation for surgery has been practiced with greater care in recent years Surgeons of today see to it that the mouths of patients are rendered as free as possible from pathogenic micro organisms before surgery is undertaken They like to have such conditions as pyorrhea and other foci of infection in the mouth and the throat brought under control before surgery is performed Even with such precautions they prefer to use local anesthesia when operations are to be done about the mouth, nose and throat so as not to interfere with the cough reflex When general anesthesia is employed, whether or not there has been time to attend to the oral hygiene, the surgeon insists that the position of the patient's head and neck be at such a low level that there is no possibility of materials from the mouth and throat being aspirated into the trachea Hyperventilation of the lungs following surgery, with insistence that the patient cough and expectorate secretions, does much to maintain good drainage The surgeon should never be denied the opportunity of having the lungs carefully examined within two or three weeks following every operation

Bronchoscopic examination should be made immediately following the suspected aspiration of any foreign body Such bodies, if allowed to remain in the bronchi, may lead to abscesses Therefore, any severe paroxysm of cough which cannot be explained on some other basis should lead one to suspect the aspiration of a foreign body A first class bronchoscopist should be called and bronchoscopic inspection permitted if and when he considers it indicated Many pulmonary abscesses can be prevented in this manner

Persons unconscious from alcohol, narcotics, injuries etc, should immediately have the head and neck placed at such a low level that there is no danger of aspiration from the mouth and throat into the trachea Elderly persons may aspirate materials from the mouth and throat during sleep Therefore, in addition to the practice of good oral hygiene they should sleep with the foot of the bed elevated four to six inches

After an attack of pneumonia the lungs should be examined with great care Failure of resolution at the proper time or the appearance of areas of atelectasis or wheezing indicate an immediate examination by the bronchoscopist At this time the removal of obstructive materials, such as mucous plugs, may prevent pulmonary abscess

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Chapter IV

THE PNEUMONIAS

BACTERIAL PNEUMONIA

By Italio F Volini, M D and
Edward J O Donovan, M D

BACTERIAL pneumonia is an infectious, inflamatory disease of the lung caused by pathogenic bacteria As a result of the ensuing exudate in the alveoli and interstitial tissue, consolidation in greater or lesser degree occurs

Bacterial pneumonia is still one of man's most serious infectious diseases The United States and most civilized countries of the temperate zones yield many cases yearly The malady stood high as a cause of death for many years in this country, but the advent of the sulfonamide drugs, and particularly penicillin, has been followed by a great drop in its mortality rate Increasingly accurate knowledge of the bacterial agents concerned in pneumonia, and the increasingly complete development of antibiotics, have led to an improved classification of pneumonia on an etiologic basis

Etiology

More than 90 per cent of lobar pneumonias are caused by the pneumococcus Approximately 65 per cent of bronchopneumonias are caused by the pneumococcus, the remainder are caused by the streptococcus and other pathogenic bacteria Pathogenic bacteria may also cause a pneumonia of the lobular distribution type, of the central or hilar type, intersitial type, aspiration type, and hypostatic type In spite of the fact that even the first sputum is not routinely examined in all hospitals, pneumonias may and should whenever possible be classified according to the causative micro-organism In order of frequency and most commonly found bacteria causative of pneumonia in ordinary times are the pneumococcus (causes most acute lung infections), streptococcus hemolyticus (2 to 3 per cent except in epidemics), Friedlander s bacillus (1 to 3 per cent), staphylococcus aureus, hemophilus

influenzae, and the tubercle bacillus Because of their different etiology and less typical course, the forms of pneumonia designated as "atypical pneumonia" will be treated under a different subject—even though confusion may be caused by the fact that the disease caused by the higher numerical types of pneumococci often runs an atypical course

Among the *predisposing factors* to pneumonia age is still important The beginning and latter phases of life are the most susceptible periods Infancy and old age do not bear the disease well and often exhibit poorly diagnostic symptoms The Negro race is apparently more vulnerable Exposure to hardships and weather, together with fatigue and debility, lowers individual resistance Sudden changes in temperature of weather may play an important role by initiating vasomotor changes in susceptible tissue Previous attacks do not prevent recurrences Most cases are initiated or preceded by an upper respiratory infection Ordinarily the disease is a sporadic one with no known source of infection, although epidemics do occur under unusual circumstances, especially where many individuals are grouped together in prolonged close personal contact It is felt that a normal carrier is the source of infection

Pathology

Consolidation of pulmonary tissue, either of a complete lobe or lobes or of scattered areas, is the essential morbid change One or more lobes may be affected, or diffuse spotty patches of lung tissue may be rendered airless In two lobe infections the most common combination is that of both lower lobes If lobar consolidation is present the affected tissue is larger than the unaffected lobes The tissue is congested and firm The stages of (1) engorgement, (2) red hepatization, (3) gray hepatization, and (4) resolution are well known Two or more stages may be demonstrable in the same case Engorgement represents congestion of blood vessels and diffusion of blood and blood products into the alveoli Red hepatization represents solidification of alveoli with fibrin, red blood cells, leukocytes and bacteria Gray hepatization represents consolidation with larger numbers of leukocytes, lesser numbers of red blood cells, many bacteria and active phagocytosis Resolution exhibits translucent jelly like tissue with the alveoli only partially filled with cells, with considerable numbers of desquamated epithelial cells, and beginning regeneration of alveolar epithelium The rare staphylococcus aureus pneumonia exhibits a bronchial type of consolidation, suppurative bronchiolitis and multiple miliary abscesses Friedlander's

bacillus infections often exhibit liquefaction of alveoli and their replacement by mucinous exudate Evidence of consolidated lung tissue is often present long after symptoms have disappeared

The spleen may undergo moderate enlargement Cloudy swelling of the liver and kidneys may be apparent Suppurative complications may be encountered in the pleura, pericardium, endocardium and other tissues

Arterial blood oxygen saturation of 75 per cent is not uncommon in severe cases of pneumonia, as opposed to a normal saturation of 95 per cent Thus the symptoms of anoxemia, which in themselves may be serious, are added to the symptoms of infection

Symptoms

The symptoms are altered by the age of the patient and the type of causative micro organism However, the great majority of cases will present a fairly distinctive picture

The *onset* is more commonly sudden but may follow upon an upper respiratory infection of some days duration Streptococcal pneumonia is more gradual in onset and usually follows a preceding infection, such as measles

A *chill* is characteristic

Pain in the chest appears commonly after the chill, and is usually in the region of the pleuritic irritation, but may be referred to the abdomen and simulate inflammation in that area

Body *temperature* ascends rapidly during the chill and usually remains high In classical lobar pneumonia or with infection by the dominant types of pneumococcus a typical temperature is a high plateau without much variation In aged individuals the fever is often lower or the temperature may pursue an almost normal course The seriousness of the infection cannot be gauged by the height of the fever

Cough initially is of a dry unproductive character, is apt to be paroxysmal and the cause of much pain With progress of the disease the cough becomes less painful and more productive of sputum

Tenacious rust colored *sputum* is quite pathognomonic of lobar pneumonia, but the color progresses to yellow and mucopurulent with the stages of gray hepatization and resolution The sputum of Friedlander's infection is more often brick red or of an appearance resembling currant jelly

Dyspnea is an important presenting symptom Respiration is usually

rapid, shallow, and painful to the inflamed pleura The respiratory rate is out of proportion to the fever An expiratory grunt may accompany especially labored breathing

Herpes is very commonly present, is seen most frequently on the lips, but may be present in other areas of the face

Delirium is manifest in about 25 per cent of cases It is exhibited particularly in alcoholic patients The mental aberration of such patients may progress to delirium tremens Children may present at the onset a convulsion and other cerebral symptoms suggestive of meningitis

Nausea and vomiting occur frequently The illness may be ushered in by such symptoms Jaundice occurs in 5 to 10 per cent Deep jaundice, which is rare, indicates toxic hepatitis, and renders the prognosis unfavorable Tympanites may be troublesome, is most marked in severe cases, and may add to respiratory distress

Physical Signs

Physical signs for the first day may not be prominent However, the general appearance of flushed face, cyanotic lips, hot skin, herpes, labored breathing, cough and rapid pulse is strongly suggestive

Shortly there will develop in most cases quite definite chest signs The earliest signs are limitation of movement of the affected side, suppression of breath sounds, and showers of fine crepitant rales

By the second or third day more fully developed signs of consolidation should be present Restriction of movement is more marked Auxiliary action of the accessory muscles may be apparent Palpation will disclose increased tactile fremitus and in some cases a pleural friction rub Dullness is found on percussion over the affected areas Skodaic resonance is sometimes elicited over uninvolved tissue just above a consolidated area The fine crepitant rales become less numerous, and bronchial breath sounds audible Should large bronchi be plugged with exudate, bronchial breathing may be absent or faint Whispered pectoriloquy and egophony are heard The heart may show dilatation of the right side, will present a rapid rate and ectopic beats quite commonly The second pulmonic sound is accentuated, and sometimes an apical systolic murmur is heard With severe toxemia the myocardium may become exhausted and present indistinct tones of a fetal character

Resolution is accompanied by a gradual change and disappearance of chest signs Moist rales of the subcrepitant type appear Resonance

reappears, and the voice and breath sounds gradually lose their bronchial quality

LABORATORY FINDINGS

Sputum should be examined in every case A microscopic examination of a direct smear will often reveal the etiologic bacteria and be a distinct aid in choice of therapy Acid fast bacilli should be looked for routinely When the cough is unproductive, a small amount of mucus may be obtained with a throat swab Bacteremia increases the gravity of the prognosis The desirability of a blood culture is therefore apparent Sputum should be obtained and blood for culture drawn before antibiotics are administered

A total leukocytosis is usually present, with a relative increase of the polymorphonuclear cells The degree of infection is more clearly determined by the shift to the left or the increase in immature polymorphonuclear cells Counts above 30 000 per cu mm suggest a suppurative complication In overwhelming infections a leukopenia may be manifested, indicating a toxic depression of the bone marrow

Urinalysis discloses a decreased output, a high specific gravity, and a trace of albumin, in many cases casts, and characteristically a decrease in the content of chlorides

Chest x ray examination discloses an opaque shadow or shadows corresponding to the sections of consolidation Roentgenologic mottling continues for a time after the physical signs have disappeared Initial films with repeated x ray examinations in the patient who is responding unfavorably are necessary

Clinical Course

With present day chemotherapy the temperature usually drops within 48 hours Without such chemotherapy the fever and toxemia may last for from 5 to 10 days, sometimes even longer Under the latter conditions the disease may terminate by crisis or lysis A pseudo-crisis may be followed by a recurrent rise in fever for approximately 24 hours In fatal cases the temperature remains high, the pulse becomes weak, and respiration continues rapid The cause of death in pneumonia is usually circulatory failure due to vasomotor paralysis Some cases will terminate fatally as a result of incidental or metastatic complications

Pneumonia Complications may be listed as follows

Pleurisy with effusion

Empyema, which may be of gravitational type or of an encapsulated type
Pericarditis in some cases with effusion of a suppurative variety
Endocarditis
Meningitis
Arthritis
Thrombosis and embolism
Peritonitis
Lung abscess
Acute nephritis
Parotitis
Otitis media
Atelectasis
Unresolved pneumonia, seen chiefly in elderly patients, and continuing for weeks or months

The Differential Diagnosis will include the following conditions with which pneumonia may be confused

Influenza
Acute bronchitis
Pleurisy
Pneumonitis of tuberculous or other types
Pulmonary infarction
Lung abscess
Abdominal conditions such as appendicitis and cholecystitis

Prognosis

The introduction of present day chemotherapy has caused the mortality of pneumonia to drop from 30 per cent or 40 per cent to below 10 per cent There will always be a minimal fatality rate in patients who have contributory debilitating conditions Infancy, old age, and bacteremia add to the gravity of the prognosis

Treatment

Pneumonia is still a serious disease, and present day chemotherapy should not blind the physician to the continued need for auxiliary supportive treatment of the malady Such supportive treatment includes

1 Rest in bed

2 Oxygen if respiration is greatly labored, if cyanosis is marked, if tympanites is present, or if the pulse rate is above 120 The tent or

chamber is the most satisfactory method of administering oxygen

3 Analgesia with salicylates, codeine, or stronger opiates as the need may indicate particularly for severe pain

4 Sedatives such as barbiturates, chloral hydrate or bromides to allay restlessness and apprehension

5 A nourishing palatable, easily digested and assimilated diet

6 Careful attention to bowels

7 Heat locally to abdomen if distention continues in spite of oxygen administration

8 Adequate fluid intake

The drug of choice against most cases of bacterial pneumonia is penicillin It exercises a highly specific effect against the pneumococcus as well as against other gram positive bacteria The drug may be administered parenterally or by mouth A crisis usually occurs in 18 to 48 hours, but the medication should be continued for five or six days lest a relapse occur If a favorable response is not induced within 48 hours, a reinvestigation of the bacteriology of the sputum and/or blood should be made If pneumonococcal etiology of the infection is again confirmed, the presence of a complicating empyema meningitis endocarditis or other lesion should be searched for by the usual investigations

The preferred method at the present time is the use of procaine long acting penicillin combined with a quantity of water soluble drug Such a preparation initiates a high blood level rapidly and prolongs its effect over a period of 24 hours or longer The initial dose is 1 cc containing 300 000 units of procaine penicillin and 100 000 units of crystalline penicillin given intramuscularly Subsequent doses which may be given every day or every 12 hours in severe infections are 1 cc of the procaine type with the crystalline addition

Plain crystalline water soluble penicillin may be used if desired It must be given often because of its rapid loss from the body An initial dose of from 40 000 to 50 000 units should be given intramuscularly and should be repeated in two hours 15 000 to 20 000 units should then be given every three hours day and night After the crisis the night doses may be omitted if desired This form of penicillin may be given intravenously if indications exist

Results of oral penicillin are very satisfactory Because of variations in individual absorption power, large doses should be given, and the drug should be administered between meals Frequent administration is again necessary The initial dose should be 200 000 units, followed in

two hours by 100,000 units Subsequently, 100,000 units is given every three hours After the crisis the night doses may be omitted Little difference in absorption is observed whether the oral preparation is dissolved in water, enclosed in a capsule, or in the form of a tablet

Members of the sulfonamide group of drugs possess a specific anti bacterial effect against the pneumococcus and other gram positive infections, although they are more toxic and inferior in potency to penicillin Sulfapyridine, sulfathiazole, sulfadiazine, sulfapyrazine and sulfamethazine are the ones used over a period of years The most popular at the present time is sulfadiazine Sulfamerazine and sulfa methazine, however, are known to be quite as effective, less toxic, and maintained longer in blood concentration so that less frequent dosage is required With all of these drugs a blood level of 7 to 10 mg per 100 cc is desirable as quickly as possible To acquire such a level and to maintain it, an initial dose of 4 grams is indicated, followed by 1 gram every four hours, except in the cases of sulfamerazine and sulfametha zine where a schedule of every six hours is sufficient The dosage should be continued for two or three days after the temperature has dropped to normal The schedule may then be discontinued, or the dose reduced to half for 24 or 48 hours If there has been an especially severe infection with or without bacteremia, the sulfa drug should be continued for five or six days after the temperature has reached normal An intravenous preparation of the sodium salt of these drugs is available for emergency use in a dosage of 5 grams Its use may be followed by intravenous admin istration of 2½ grams every eight hours The use of alkaline therapy in sufficient quantity to maintain the pH of the urine at 7 5 or above is recommended to prevent crystalluria and urinary irritation or obstruction Sodium bicarbonate, or an equivalent alkali, in an initial dose of 6 grams and subsequent doses of 2 6 grams with each dose of the sulfa preparation is advised when the oral drug is used The intravenous sulfa preparation may be given in one liter of M/6 sodium lactate solution Blood sulfa levels, if possible, should be determined daily for two or three days Daily urinalysis and blood counts are advised because of the toxic effects of the sulfonamides on the urinary tract and bone marrow The combined use of penicillin and sulfa preparations against pneumonias of gram positive bacterial origin, in the light of present day knowledge, is unnecessary

For infections caused by Friedlander s bacillus, hemophilus influenzae, the tubercle bacillus, or gram negative organisms, the use

of streptomycin is recommended The dihydro preparation is preferred because of its lesser toxicity, especially upon the auditory nerve Recommended dosage is 2 to 3 grams per day in divided portions of 0 25 grams intramuscularly every three hours until the infection is under control Sulfadiazine possesses efficacy against Friedlander's bacillus, and may be used if the use of streptomycin is contraindicated, or a combination of the two drugs may at times be indicated

The experience at the present time would seem to indicate effectiveness of the two newer antibiotics, aureomycin and chloromycetin in the control of bacterial pneumonia One gram or four capsules initially with one half gram every three hours has been the dosage schedule which we have employed Also, terramycin is useful when administered orally in the form of 0 25 gm capsules The initial dose is 2 0 gm, followed by 1 0 gm every six hours Further experience is definitely necessary properly to list these antibiotics for their effectiveness

PRIMARY ATYPICAL PNEUMONIA

By ITALO F VOLINI, M D AND EDWARD J O DONOVAN, M D

Primary atypical pneumonia is not a new disease As a clinical entity now sufficiently well defined to be recognized, the variations in the clinical pattern and course may vary extensively The absence of an easily isolated etiological agent or a readily applicable laboratory test does *not permit easy clinical diagnosis The multiplicity of synonyms* employed to name this entity indicates that uncertainty exists often in its diagnosis

The disease has aroused interest because of an apparent increase in frequency in recent years The malady has frequently been termed *virus pneumonia, acute interstitial pneumonitis* and *bronchopneumonia variety* Widespread epidemics were observed before the war and during the war years In one period of little more than a year 26,000 Army personnel were reported to have been afflicted The clinical picture has been made clearer by observations on many groups of cases Owing to causation by different types of viruses and because the pneumonia may be part of a more widespread systemic disease there are often grada tions of severity of the illness Overwhelming evidence has been presented however, that the vast majority may be caused by a virus previously not isolated and unrelated to other viruses

Etiology

The causative factor in atypical pneumonia is *therefore a virus* There is very general agreement that the large epidemics studied between 1940 and 1944 were caused by an agent not previously isolated It is recognized that a number of viruses may cause pneumonia, includ *ing influenza virus A and B, the viruses of ornithosis* lymphocytic chorio meningitis virus and mouse pneumonia virus The results of studies indicate, however, that all these known viruses together have been responsible generally for only a very small proportion of the cases of atypical pneumonia, and suggest that the etiology of most cases must be explained by the isolation of new viruses Pulmonary consoli dation has been produced in hamsters and cotton rats when inoculated by the intranasal route with suspensions of amniotic membranes, lungs and tracheas of chick embryos infected with filtrates of sputum or lung from a fatal case Neutralization tests with serum from active cases of atypical pneumonia have shown that the serum in the acute phase has a low titer of neutralizing antibody and that convalescent serum fre

quently causes neutralization in a high titer A smaller proportion of patients with febrile upper respiratory infections occurring during the course of atypical pneumonia epidemics have shown an increase in neutralizing antibody

Pathology

Since the fatality rate has been so low, available data on tissue morbidity are scanty The features common to most cases are acute bronchiolitis and interstitial pneumonitis The pleura remains smooth, and large pleural effusions are seldom observed The extent of parenchymal involvement is variable Cut surface of the affected lung shows a nodular appearance owing to the prominence of thickened bronchiolar walls and extruding purulent exudate Microscopically, the bronchioles show desquamation of the mucosa and filling of the lumen with polymorphonuclear exudate, the peribronchiolar areas reveal dense aggregations of round cells, the alveoli show cellular infiltrations and edema in their septa and a cell content in their lumina varying from scanty to profuse and composed of either predominantly mononuclear cells or mixed mononuclear and polymorphonuclear cells There is a striking contrast between the more frankly polymonphonuclear bronchiolar exudate and the predominantly mononuclear alveolar exudate.

Clinical Course

The disease is transmitted from human being to human being by the respiratory route The incubation period ranges from 5 to 25 days, is most frequently between 10 and 14 days The malady is moderately communicable, but many exposed persons do not develop pneumonia Epidemics are often prolonged, and the largest outbreaks have occurred among recently inducted military personnel and in student groups The duration of immunity after one attack is not established

The onset is usually gradual The symptoms increase in severity over a period of one to two days The symptoms are sensations of fever, chilliness, cough, malaise and headache Upper respiratory symptoms are less common Retrosternal pain is not infrequent and may be aggravated by cough Sharp pleuritic pain is quite infrequent

Examination shows the patient to appear slightly to moderately ill Except in the case of influenzal pneumonia, there is less prostration than in the similar stages of bacterial pneumonia The mind is quite clear Cough is variable, may be persistent and troublesome or quite

infrequent. If there has been no pre-existing respiratory disease, sputum is scanty and mucoid, occasionally exhibits bloody streaking. The pharynx is usually injected. Lymphadenopathy is not notable. Chest examination in the first several days of the illness may disclose small patchy areas of decreased resonance and subcrepitant rales. Absence of chest findings, however, is not uncommon. The temperature ranges between 99° and 105° F, but is usually between 100° and 103° F. Little dyspnea or cyanosis is shown. The respiration and pulse rate are normal or moderately increased. Transient severe sweats occur in some cases.

The full course varies from mild to moderately severe, or in a few cases, to a fatal termination. Most patients never appear severely ill, although frequently quite uncomfortable. The fever attains a maximum within several days and then falls by lysis over a period of from 5 to 10 days. After that time physical and x-ray findings may become more prominent, but the patient's symptomatology improves steadily. Except that the cough increases by becoming more productive, recovery is then relatively rapid. Relapse may occur as a result of extension of the original pneumonic process or of involvement of new areas of lung, but is relatively uncommon.

Approximately 20 per cent of cases are seriously ill. Fever is prolonged and may be sustained or intermittent in character. Physical findings are more definite and may indicate outright widespread consolidation. Dyspnea and cyanosis may be prominent. Mental clearness usually remains, however. Recovery in this type may be gradual and prolonged.

In less than 1 per cent of cases progression of the pneumonic process continues steadily until most of both lungs is involved. Symptoms in such patients are extreme, and there may be varying degrees of vasomotor collapse. Thus a fatal outcome may ensue.

Laboratory Aids

Sputum examination shows an exudate which is poor in cells but in which mononuclear cells predominate. There are few bacteria visible. The virus of psittacosis may be isolated from the sputum or, in early cases, blood. The rickettsia of Q fever may be recovered from the blood *during the acute phase of the disease.*

The majority of total white blood counts and differential counts are normal. Many show a leukopenia. A very few are above normal, but

counts exceeding 12,000 per cu mm are exceptional unless there is a concurrent bacterial infection With advance of the disease the white count may rise, and some seriously ill and fatal cases have shown exceedingly high counts

The sedimentation rate of the red blood corpuscles is accelerated early, returns gradually to normal during the period of recovery

X ray films will show areas of increased density in the lung fields These areas are often out of proportion to the physical findings and to the clinical complaints Classically they are observed first in the hilar regions and extend from there peripherally into the lung parenchyma Shadows may be patchy or may be of a fairly uniform haziness The density of the shadow is less than that of untreated bacterial pneumonia The lower lobes are more affected and frequently bilaterally Antero posterior films may fail to reveal small areas of infiltration in the hilar and basal regions which may be more clearly demonstrated in lateral or oblique films The migratory extension is noted in the more severe types of the disease when controlled by repeated x ray films

Significant titers (40 or more) of cold hemagglutinins are found in the serum of between 50 per cent and 60 per cent of patients with primary atypical pneumonia The agglutinin titer begins to rise between the 7th and 14th day after onset, attains a peak about 21 days after onset, then falls off rapidly Though cold agglutinins are found in a very large majority of diseases their occurrence in acute respiratory infections other than viral pneumonia is infrequent Increase in titer has been observed in influenza, with or without pneumonia, but this is rare There is evidence that suggests that the percentage of positive results is low in patients who have only a mild illness and high in those who are moderately or severely ill

Streptococcus MG agglutination in a titer of 20 or more is said to occur in almost 50 per cent of cases of primary atypical pneumonia, whereas the test is positive with such a titer in only 5 per cent or 6 per cent of normal individuals or patients with other diseases The explanation for the occurrence of agglutinins and other antibodies for this streptococcus is not yet clear

A differential diagnosis of atypical pneumonia includes consideration of the following conditions

Bacterial pneumonias
Influenza
Tuberculosis

Coccidioidal pneumonia and other mycotic pneumonias
Pulmonary infarcts
Transient bronchopneumonia occurring in patients with bronchogenic carcinoma or bronchiectasis
Loeffler s syndrome and tropical eosinophilia
Certain lung abscesses

Treatment

The therapy of primary atypical pneumonia has been largely symptomatic Sulfonamides, penicillin, and streptomycin do not alter the *course of the disease Penicillin is usually given a trial for several days* Aureomycin or chloromycetin in full therapeutic doses, two grams initially and 500 mg orally every four hours, is now claimed favorably to alter the course of the disease Also, terramycin may be prescribed in the same manner as for the treatment of bacterial pneumonias

In all forms of the disease symptomatic and nursing care remains important Steam inhalations are valuable if cough is distressing *Codeine or other opiates may be necessary to suppress the cough or to* quiet severe pain Salicylates are of value for the relief of headache and general distress and to combat high fever Oxygen may be required for seriously ill patients Malnutrition and intestinal distention should be guarded against Rest in bed is important, and the period necessary for convalescence is often long

RHEUMATIC PNEUMONIA

By ANDREW L BANYAI, M D AND J WINTHROP PEABODY, M D

It is a well established fact that specific pneumonia may occur during the course of rheumatic fever Its incidence varies from one to over 10 per cent Swift and also, Lichtwitz advanced the concept that the pulmonary lesion is not caused by any particular micro-organism but it is the result of sensitization to a protein antigen derived from bacteria Generally it is assumed that group A hemolytic streptococcus is implicated Rich was able to reproduce identical pathologic changes in experimental animals He proved that these changes were manifestations of an allergic response to circulating antigens

A precise description of the characteristic histopathologic changes is available in the writing of Gouley His studies revealed the following findings

1 *Acute rheumatic pneumopathy* 'The initial destructive phase is characterized by foci of fibrinoid necrosis in the alveolar walls with cellular infiltration of monocyte variety, apparently of reticular and endothelial capillary origin In severe cases of rheumatic pneumonia the alveolar walls may be converted literally into 'ribbons' of fibrin The congested capillaries often undergo a hyalin thrombosis and lose their integrity Cellular infiltration into the alveoli is usually scant consisting of phagocytes, desquamated alveolar cells and occasional neutrophils The second or proliferative phase is marked by the infiltration of larger basophilic cells, often with vesicular nuclei, sometimes multinucleated, they are the so-called 'Aschoff' cells, often in perivascular groups, spreading out into the interstitial tissues The third stage, which we assume to be a reparative reaction, consists of the presence of infiltrated plasma cells and lymphocytes, and proliferated fibroblasts'

2 *Subacute rheumatic pneumonitis* "The subacute phase is a continuation of the reparative process It is featured by 1) Marked changes in the consistency of the involved lung tissue, and 2) Basal atelectasis (inconstant) The subacutely inflamed lung, although not consolidated remains poorly aerated and often should a whole lobe or a large part of one be involved, is somewhat smaller than normal The color varies from dark red to reddish (rusty) brown and the subpleural lymphatics are often prominent as a gray web Microscopic examination reveals early

diffuse interstitial fibrosis, replacing the monocyte macrophage infiltration"

3 Chronic rheumatic pneumopathy "The lungs will commonly show a denser consistency, and usually remain semi inflated on removing the chest plate They may be grayish or else reddened in varying degree of congestion Histologic examination of the gray semi rigid or 'rubber oid' lung will show the alveolar walls thickened with collagenous fibrosis the extent of which may vary greatly even from field to field in the same section, perhaps involving large areas uniformly More often a portion of an alveolar septum will be replaced by fibrous tissue yielding in the aggregate a patchy involvement rather than a diffuse and com plete interstitial fibrosis"

Symptoms of pulmonary involvement may make their appearance after the development of polyarthritis or in association with the mani festations of carditis Clinically, three forms of rheumatic pneumopathies are recognized 1) subclinical, 2) benign, 3) severe The subclinical type represents very slight, interstitial involvement Symptoms attributable to the lung lesion are few, irrelevant or entirely absent Deviations from normal physical findings over the lungs are difficult to detect X ray changes are slight In the benign form, constitutional reactions as well as objective findings are not pronounced Percussion and auscultation detect changes characteristic of infiltration Rarely, one may find con solidation not unlike that seen in pneumococcus lobar pneumonia Rales are few in number Roentgenograms of the chest show areas of infiltra tion, usually of limited extent Occasionally, lobar consolidation may be found Lesions of limited extent have a tendency to disappear rapidly (fleeting, transitory, migratory infiltration) and then reappear again in another lobe As a rule, the temperature is irregular and only mode rately elevated In rare instances, it may rise as high as 105° F Cough may be absent, when present, it is either unproductive or the patient expectorates small amounts of white, tenacious, nonpurulent, blood streaked sputum Chest pain is infrequent It occurs in association with pleural involvement or pericarditis Pleural effusion and massive atelec tasis are possible complications

The most prominent symptom of severe rheumatic pneumonia are pronounced dyspnea and cyanosis These are readily explainable on the basis of widespread destruction and thickening of the alveolar septa fibrinous pseudo membrane in the respiratory bronchioles and alveolar ducts, accumulation of exudate in the alveoli, congestion and fibrosis

Needless to say that serious cardiac changes are bound to aggravate the respiratory distress and anoxemia to an alarming degree Cough and expectoration are of the same type as in the mild form Fever may reach 105° F Physical findings are usually less impressive than the extent of disease found on x ray examination

In any of the three types of rheumatic pneumopathies the combination of the following x ray changes may be anticipated 1 Enlargement of the hilar vascular shadows with fan like radiation toward the periphery ('butterfly pattern) 2 Bilateral, disseminated nodular shadows 3 Ill defined, moderately dense, parenchymal infiltrations, with wide, more or less symmetrical multilobar localization on both sides 4 Increased radiotranslucency at the lateral peripheral areas of the lung fields 5 Possible changes arising from complications, signifying the development of pleural effusion or atelectasis

The presence of rheumatic fever is a prerequisite of correct diagnosis It happens only very rarely that rheumatic pneumopathy precedes the well known manifestations of rheumatic fever In the differential diagnosis, it is mandatory to rule out other forms of pneumonia (bacterial, viral, rickettsial, parasitic) Competent bacteriologic and other diagnostic studies are indispensable Also, one must exclude diseases which may present similar roentgenologic appearance A list of conditions which may be associated with widespread miliary nodulations in the roentgenogram is given in the section on Pleuropulmonary Manifestations of Lupus Erythematosus It is especially important to distinguish rheumatic pneumonia from acute pulmonary edema In the latter, fever is moderate or absent, the sputum is pink and frothy

Kuzma and Lustok reported a case in a 6½ year old girl in which an acute fulminating lobar pneumonia occurred 20 days after the onset of rheumatic heart disease, with death in 23 days

The prognosis is favorable in the subclinical and benign forms In the latter, the pulmonary changes are likely to disappear completely in from four to 14 days The duration of the severe form is from one to six weeks The outcome is usually fatal

Treatment of rheumatic pneumopathies is supportive and symptomatic as described in the sections on Bacterial and Viral Pneumonias Salicylates and antibiotics exert no beneficial influence on their course

Promising results from the use of ATCH (adrenocorticotropic hormone) and cortisone in rheumatic fever should stimulate special studies with reference to rheumatic pneumopathies

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ORNITHOSIS

By ANDREW L BANYAI, M D AND J WINTHROP PEABODY, M D

Ornithosis is used in this text as an inclusive term which designates pulmonary disease acquired from infected parrots, parrakeets and other rare birds of the parrot family (psittacosis) and also from diseased pigeons and other possible avian vectors of this disease The latter group includes finches, sparrows, buntings, linnets, thrushes, Italian cardinal bird, canaries, love birds, arctic fulmar and other petrels, sea gulls, ducks and chickens According to the observations of Meyer, and Olson and Treuting, the disease is transmissible from man to man

Experimental ornithosis can be produced in animals by inoculation with infected fecal droppings of diseased birds For this reason, it is reasonable to assume that human infection may take place through the inhalation of infected dry droppings when the latter are blown about by air currents as dust from cages, lofts and feathers of sick birds This assumption implies the possibility of contracting ornithosis without direct handling of diseased birds In view of this it is not surprising that consternation developed when it was reported that from 40 to 50 per cent of pigeons were infected with the causative organism of this disease As a matter of fact the Philadelphia Department of Health declared in 1945 that the city s public pigeons are a menace to public health A city ordinance based on this decision permits trapping and killing of these birds by authorized agencies From all available information, it seems that there is no valid reason for such alarm or radical action from the standpoint of public health As it was pointed out in an editorial of the *Journal of the American Medical Association* (November 17, 1945), actual studies show that the risk of contracting ornithosis is not significant by inhaling dust of streets and parks where flocks of pigeons gather and their droppings soil the surroundings It is more realistic to think of ornithosis as an occupational hazard in individuals who are pigeon fanciers or keep an aviary as a hobby Also, persons who pick up or clean sick pigeons, ducks or chickens may contract ornithosis Cases have been reported in laboratory workers and in individuals in attendance of patients with ornithosis The earlier belief that one fourth of the sporadic cases of so called atypical pneumonia are cases of ornithosis has been proved to be erroneous Meiklejohn and his colleagues (1944) ascertained that evidence of ornithosis by the comple-

ment fixation test or by the isolation of the causative organism was obtainable in only 6 per cent of such cases

Ornithosis is caused by a virus which is from 0 2 to 0 3 microns in size It can be cultured on the chorioallantoic membrane of developing chick embryo With proper technique, it can be isolated from the patient s sputum and blood Post mortem examinations show that the pulmonary involvement in this disease is characterized by typical findings The cut surface of the lung is reddish gray and slightly granular The affected areas of the lung have a uniformly gelatinous consistency The bronchial mucous membrane is congested and edematous There is *a predominantly monocytic infiltration of the bronchial walls* The bronchial lumens contain considerable serous exudate There are pronounced monocytic infiltrations and congestion of the pulmonary interstitial tissue Polymorphonuclear leucocytes are only occasionally seen The alveolar walls are greatly thickened Consequently, there is a partial or complete obliteration of a great many alveoli The alveolar lining membrane is hypertrophied Numerous alveoli are filled with serous exudate, desquamated alveolar lining cells, mononuclear cells and a few polymorphonuclear leucocytes Pleural effusion is a very rare complication

Ornithosis has not been observed in children less than 10 years of age In a large group of cases investigated by Meyer and Eddie, only 13 5 per cent of the patients were between the ages of 10 and 19 years *The incubation period of ornithosis varies from eight to 14 days* Symptoms of the disease are Intermittent chilly sensations or definite rigors, grippy sensation and fever that may reach from 103° to 105° F (39 4° 40 5° C) Fever is usually the highest during the first week and it has a spiking character Later on, it is more likely to be remittent The duration of the fever is from one to five weeks Other symptoms include weakness, malaise and obstinate frontal or occipital headache not relieved by standard doses of analgesics From the head the pain may radiate along the spine, or there is lumbar backache or generalized muscle pains *Complaints suggestive of polyarthritis are rarely* encountered The same holds true of chest pain On the other hand, abdominal discomfort is common It is associated with anorexia, nausea and occasionally with vomiting Also, drenching perspiration is a frequent symptom Epistaxis occurs in about one fourth of the cases Slight photophobia and pain in the eyes may be noted too In severe cases, apathy, prostration, somnolence, sopor, stupor, delirium and other toxic cerebral

symptoms may be observed Cough is a frequent complaint, but in some instances, it is virtually absent It may be unproductive or associated with only scanty expectoration In other cases, the patient expectorates large amounts of thick, viscid, mucoid sputum

In an attempt to establish the diagnosis, the possibility of exposure to diseased birds should be thoroughly explored As mentioned before, parrots are not the only birds capable of transmitting the disease. Absence of proof of exposure to known source of infection does not rule out ornithosis Depending upon the extent of lung involvement, moderate or marked cyanosis, with corresponding degrees of dyspnea, is noted There is a disproportion between the level of temperature and the pulse rate, with relative bradycardia The tongue is often heavily coated Rose spots and petechiae in the skin may be seen at the end of the first week Auerbach and Ink observed a peculiar skin eruption in their patients with ornithosis It consisted of more or less thick pearl colored spots varying from pin point size to 2-4 mm in diameter These skin changes persisted for from 20 to 40 days The abdomen is distended The liver may be palpable, rarely, also the spleen

Physical findings over the chest are not characteristic In patients with mild and moderate forms of the disease, deviations from normal are slight or entirely absent During the early phase of the disease, the central location of the pulmonary lesion obviates its detection on physical examination With the progress of the disease, larger areas of infiltration and consolidation are recognized by impaired percussion note or dullness There may be hyperresonance over areas adjacent to the lesion The breath sounds are diminished or faintly bronchial in character There are showers of subcrepitant rales The voice conduction is increased over the involved area Friction sound indicative of fibrinous pleurisy and signs suggestive of pleural effusion are rarely found

The roentgenologic appearance of ornithosis varies from unilateral or bilateral increase of the hilar shadows to widespread patchy infiltration of all lobes Other possible manifestations in the roentgenogram are as follows

(1) A fan shaped infiltration spreading from the hilum toward the periphery

(2) Round or irregularly outlined shadow at any region of the lung Such lesions reach their maximum development in three to four days, then they may disappear entirely, leaving clear lung behind, only to be followed by similar involvement in some other zone of the same

lung or on the opposite side This type is aptly designated as creeping pneumonia

(3) Consolidation of one lobe or one lung, characterized by uniform, heavy density over extensive lung areas

Laboratory studies are indispensable in arriving at the correct diagnosis *Complement fixation test with the patient's serum was first* proved to be of diagnostic value by Bedson and his associates in 1930 Since then, its merit as a conclusive test has been well established During the course of the disease, there is a pronounced increase in the titer The latter gradually decreases during the subsequent months Rivers and his collaborators (1930) showed that it was possible to confirm the diagnosis by inoculating white mice with the patient s sputum It is possible to isolate the causative virus from the patient s sputum and blood to the tenth day of the disease Meyer and Eddie, whose outstanding accomplishment is generally recognized relative to the diagnosis of this condition emphasize the importance of these laboratory procedures They say

> It is imperative that in the future at least two criteria be adopted in the diagnosis of psittacosis
>
> (1) Isolation of the virus from the blood or sputum during the acute phase, and
>
> (2) The demonstration of a significant rise in titer in complement fixing antibodies
>
> Blood collections taken during the acute phase of the disease may be of diagnostic assistance if used in making animal inoculations and serologic tests Certainly, no effort should be spared in the attempt to isolate the virus Modern technics *which destroy concomitant bacteria encourage the use of nasal* or throat washings, should the nonproductive cough fail to yield suitable specimens Again, vomitus or gastric lavage specimens may be successfully injected into mice and examined for virus Repeated examinations of serum samples collected during the first week of illness for complement fixing antibodies may supply suggestive information A two fold to four fold increase in titer, for example from 1 2 to 1 8 + + + +, together with objective signs of pulmonary involvement warrants *an early tentative diagnosis of psittacosis and the prompt* institution of specific therapy[1]

Routine white blood cell count rarely shows leucocytosis, rather,

there is a tendency to leucopenia In the differential white blood cell count (Schilling), there is a pronounced shift to the left, signifying an increase in the number of juvenile neutrophile leucocytes When leucocytosis is found, it should be considered suggestive of secondary infection The sedimentation rate of the erythrocytes is increased There may be slight albuminuria

In the differential diagnosis, one should rule out typhoid fever, infection with salmonella, brucellosis, rickettsial and virus infections, including so-called atypical pneumonia and influenza, tuberculosis and fungous diseases of the lung bronchopneumonia and lobar pneumonia caused by common pathogenic micro organisms, acute interstitial pneumonitis and pulmonary adenomatosis Moreover, conditions should be excluded which are associated with fever and in which pulmonary changes cast a round shadow in the roentgenograms These are enumerated in the chapter on Pulmonary Adenomatosis

Prior to the introduction of specific therapy in the form of penicillin and aureomycin, the mortality of ornithosis varied from 10 to 45 per cent Fatal termination was especially high in older individuals Without specific treatment, the course of the disease lasts from one to two weeks in mild cases and from two to five weeks in severe cases The therapeutic value of penicillin in experimental ornithosis was discovered by Heilman and Herrell in 1944 Subsequently, the clinical value of this drug has been firmly established by the studies of Turgasen, Flippin and his co workers, Rubinstein and his colleagues and others The usual method of treatment is to give 300,000 to 400 000 units of penicillin daily until three or four days after the patient s temperature returns to normal With the administration of penicillin fever disappears, symptoms and objective findings improve in from 24 to 48 hours

Aureomycin is administered orally in doses of 25 to 50 mg per kg of body weight per day for moderately severe cases In severe infections, from 50 to 100 mg of aureomycin are given per kg of body weight per day for five days or longer The drug is administered every four hours the first day, from then on, every six hours Also, chloramphenicol is of value It is given in doses of 50 mg per Kg of body weight per day, in divided doses at four to six hour intervals

In addition to specific medication, general supportive and symptomatic measures should be instituted as required by the patient s condition These should cover the maintenance of fluid and electrolyte

balance, adequate nutrition, vitamin intake, the management of cough and the control of other disturbing symptoms

Hurst and his associates reported experimental psittacosis in the mouse with aureomycin and terramycin highly and equally effective, massive doses of procaine penicillin less active, chloramphenicol indifferently active A combination of penicillin and aureomycin gave inferior results to either one alone There was limited recurrence after treatment ceased The subjects were observed for 35 to 50 days

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PLEUROPULMONARY TULAREMIA

By Andrew L Banyai, M D and J Winthrop Peabody, M D

The name of this disease is derived from Tulare County in California where the first systematically identified human cases were observed For this, credit is given to Francis, who published his report on this subject in 1922 In doing so, it is recognized that Pearce, of Utah, observed a number of patients with this disease as early as 1908 and reported on them in 1911

The causative micro organism of tularemia, Pasteurella tularensis or Bacterium tularense, is a gram negative, aerobic bacillus which has been found in a great variety of wild and domestic animals From the standpoint of pathogenesis and diagnosis, familiarity with the possible source of infection is of importance It is generally accepted that about 90 per cent of human tularemia is contracted from wild rabbits through contact with infected animals The infection is usually transmitted by handling or skinning contaminated rabbits Eating insufficiently cooked meat of these animals may also be the cause of human infections There are regions where the disease can be traced to tick bite, to the bite of horse flies or deer flies

The following are known vectors of P tularensis Dog tick (Derma centor occidentalis and Dermacentor variabilis), wood tick (Derma centor andersoni) and the sheep tick (Melophagus ovinus) Tick bite as the source of infection may be as high as 90 per cent Also, it has been demonstrated that tularemia may be water borne and acquired through drinking from contaminated streams Animals in which P tularensis has been found include beaver, cat, coyote, deer, dog, fox, hog, ground hog, meadow mice, mink, muskrat, opossum, raccoon, rat, skunk, squirrel, weasel quail, sage hen, bull frog With so many potential carriers of the pathogenic micro organism, exposure may take place *through handling their meat or pelt In this manner, people who are* professionally engaged in handling these animals or come in contact with them through the urge of outdoor life, are the most likely victims of tularemia To these groups of individuals belong sheep herders shearers, hunters, trappers, campers and woodsmen Unfortunately, the disease may strike those who do not suffer from wanderlust, but inadver tently happen to handle infected animals This group of persons includes market men butchers, cooks and housewives A recent impetus to the increased incidence of tularemia has been brought about by the popular

acceptance of frozen food lockers built for the home These undoubtedly encourage home butchering and large scale storage of raw meat It can be appreciated that tularemia is not restricted to rural communities With the present day marvelous means of facile and rapid transportation, people living in large urban communities have easy access to pastoral and sylvan regions or may be exposed to contaminated material sent to the cities Laboratory workers who handle animals used for diagnosis or specimens for experimental or diagnostic purposes are facing a hazard of infection in case of some technical accident

Since the time tularemia was first identified as a clinical entity in California, cases have been reported from every state of this country and from a number of foreign countries It occurs with equal frequency in exposed males and females, in the white and Negro and at any age period It is a systemic disease which develops with certain dominant clinical manifestations On this basis, earlier observers described the following types

(1) Ulceroglandular
(2) Oculoglandular
(3) Glandular
(4) Typhoidal

The classical pattern of the disease consists of an ulcer that develops at the primary site of infection This is followed by a rapid swelling (bubo) of the regional lymph nodes Next to lymph nodes the lung is the most common organ involved after the primary infection Pleuro pulmonary involvement is encountered in about 60 per cent of ulcero glandular, 34 per cent of the so-called typhoidal and 6 per cent of the glandular forms of tularemia It is estimated that pneumonic consolida tion occurs in about 20 per cent of all clinical cases of this disease Post mortem examinations reveal pulmonary involvement in more than 60 per cent

The incubation period of tularemia varies from one to seven days Morgan found that tularemic pneumonia developed in nearly 60 per cent of the cases without detectable primary site and secondary lympha denitis Such instances are considered cryptogenic This term is preferable to primary pulmonary tularemia There is no proof that the latter ever occurs Pathologic examinations show that the pulmonary lesion is nodular, granulomatous in character, with a tendency to con fluence and focal necrosis Grossly, the involvement is seen in the form of segmental (bronchopneumonic) or lobar lesion Both lungs are fre

quently affected simultaneously A cavity (abscess) may result from focal necrosis Cavities may be single or multiple Histologic studies show an intense inflammatory process in the consolidated areas The inflamma tion involves the alveolar spaces, interstitial spaces, small vessels and small bronchi *The pulmonary exudate contains mostly monocytes,* lymphocytes, histiocytes and plasma cells Polymorphonuclear leucocytes are rare unless secondary infection sets in The inflammatory process is associated with the production of much fibrin and edema of the walls of the small vessels Consequently, the latter become narrowed and thrombosed Fibrous proliferation may be found in the wake of the foregone inflammatory changes According to Blackford and Casey bronchitis occurs in 10 per cent of patients with tularemia without the presence of pneumonia There is considerable peribronchial infiltration in such cases Also, occlusion of the narrowed bronchial lumen by accumulated tenacious mucopurulent exudate is bound to result in atelectasis of varying extent Moreover, bronchiectasis may develop in consequence of inflammatory changes in the bronchial wall, fibrosis, or both Rarely, necrotic involvement of the visceral pleura leads to spon taneous pneumothorax or hydro-pneumothorax Enlargement of the hilar lymph nodes, sometimes to a considerable extent, is a common occurrence

Pleurisy occurs in two forms during the course of tularemia in over 10 per cent of the cases

(1) Plastic

(2) With effusion

The latter was first observed by Verbrycke in 1924 Necropsy reveals small whitish nodules, fibrinous strands between visceral and parietal pleurae, thick, greenish, fibrinous or fibropurulent exudate covering the visceral pleura Clinically, as well as on post mortem examination, one finds small or large quantities of effusion in about three per cent of the patients The effusion may develop as a complication of tularemic *pneumonia or without pneumonia In some instances,* the appearance of the effusion precedes that of pneumonia Blackford and Casey called attention to the fact that when pleural effusion complicates tularemic pneumonia, the development of the former is slower than that of effusion which follows pneumococcic pneumonia As a rule, the pleural fluid is characteristic of inflammatory origin Its specific gravity is 1 015 or over and contains from 2,000 to 5,000 cells per cubic millimeter, rarely over 10,000 The differential count usually shows a preponderance

of polymorphonuclear leucocytes (from 60 to 80 per cent) There are instances where over 90 per cent of the cells are made up of lymphocytes as it is often seen in tuberculosis The effusion is clear or slightly turbid, of amber, straw, greenish yellow or orange color Rarely, it is sanguineous

Symptoms

The onset of symptoms is sudden or insidious in tularemic pneumonia In acutely developing cases, the patient shows the well known toxic manifestations of the disease, such as chills which may be severe, fever between 102 and 104° F, which in some cases reaches 106°, drenching sweating, malaise, generalized aches, headaches, prostration, nausea, vomiting, drowsiness, possibly, stupor and coma and occasionally, delirium Local symptoms include chest pain, which is often sharp, knife like, harassing cough and dyspnea Cough is unproductive at first Expectoration begins usually toward the end of the first week of illness The sputum is thick, tenacious, white or pale yellow, mucoid or purulent in character Occasionally, it is blood tinged Frank pulmonary hemorrhage may also occur In the presence of large pulmonary abscess, there is excessive expectoration

In patients with bronchitis, constitutional symptoms are usually less pronounced Cough is noted a few days after the infection It is unproductive in about one third of the cases Cough in these cases may persist for months or even years The reason is the fibrosis and bronchiectasis that may follow the acute phase of the disease

With pleural involvement, pain in the chest is the presenting symptom, in addition to general toxic manifestations Affection of the diaphragmatic regions of the pleura may cause severe radiating pain in the abdomen, in the neck and in the shoulder region

Diagnosis

It is well to emphasize the utmost importance of the patient s history in this connection One must possess not only an inquisitive mind but also a thorough knowledge of the manifold possibilities of contracting this disease The patient in some instances virtually delivers the diagnosis in relating the story of hand injury which is followed by the development of a stubborn ulcer, swelling of, and abscess formation in the lymph nodes at the elbow and in the axilla In more than one half of the cases with pneumonia, however, one finds no evidence of ulcer, superficial infection of the skin, or bubo

In patients with pneumonia, it is noted that the face is flushed, respirations are short and rapid, lips and fingers show slight or pronounced cyanosis. The fever is irregular, intermittent and disappears by lysis in untreated cases. The pulse is relatively slow. Stiffness of the neck is occasionally observed. The spleen and liver are frequently palpable. In some instances, there is generalized enlargement of the lymph nodes and occasionally, ocular manifestations of the disease. Physical signs are found over the lung *from 10 days to two weeks after infection* has taken place. These consist of impaired or dull percussion note over circumscribed areas, with distant or bronchovesicular breath sounds, showers of moist rales and increased voice conduction. One may detect sonorous and sibilant rales throughout both lungs in association with pneumonic consolidation in one lung.

It is well to recognize the limitations of physical examination of the lung. Findings by this method may be entirely negative while x ray films reveal a clear cut lesion from a few days to two weeks after the inception of the disease. Depending upon the extent of involvement, roentgenologic changes are seen in one or both lungs. Usually, enlargement of the hilar shadows, unilaterally or bilaterally, is the first manifestation. This is followed by the appearance of x ray shadows indicative of segmental consolidation. Confluence of these segmental opacities may result in *a lesion which occupies a lobe, one lung or the lower two-thirds* of both lungs. In other instances increase in the size of the hilar lymph nodes and signs of pulmonary consolidation are visualized simultaneously. Frequently, there is concomitant accentuation of the bronchovascular markings. This is brought about by specific inflammatory involvement of the bronchi and by coexistent peribronchial atelectasis. Identical x ray changes are found in patients with tularemic bronchitis and peribronchitis, without pneumonia. Bronchial disease, with or without accompanying pneumonia, may result in permanent fibrosis of the peribronchial structures and in a consequent impairment of the respiratory function. Single or multiple areas of rarefaction within the consolidated lung signify cavity formation. In untreated cases roentgenologically demonstrable complete resolution may be noted in six weeks. Pleural effusion is recognized from the presence of a rather dense shadow over the lower lateral portion of the hemithorax. Its appearance is roughly triangular when the amount of effusion is moderate. Large effusions obscure the entire lung field on one side. Occasionally, evidence of pleurisy is found bilaterally. According to Hitch

and Smith, papular, macular or erythema multiforme exudativum like skin eruptions occur in 8 per cent of patients with tularemia

Agglutination test with the serum or pleural effusion is the most important means in the diagnosis of this disease Agglutination is con clusively diagnostic in a dilution of 1 80 With the usual laboratory technique, the agglutination test is read after 18 to 24 hours' incubation period Delay in diagnosis on account of this has been completely eliminated by the method of Damon and Johnson After antigen has been added to the various dilutions of serum, the test tubes are shaken vigorously, either by hand or by a mechanical shaker, for about five minutes, and then the results are read Unfortunately, the value of the agglutination test is limited by the fact that it is always negative during the first week after infection, at a time when one is most desirous of establishing a definite diagnosis Positive agglutination test is found from the eighth day on, but in some instances, it cannot be detected until the end of the sixth week This circumstance makes it mandatory to repeat this test as many times as the reasonableness of diagnostic sus picion dictates When once a significant agglutination test is noted, its titer is bound to increase rapidly to dilutions of 1 2560 and higher Its maximum is reached from the fourth to seventh week of the disease From then on, a positive aggulutination test is present for years in grad ually decreasing titers This is an important point to remember from the point of view of differential diagnosis of some subsequent obscure febrile disease of the same patient The rise of agglutination titer is not influenced by the therapeutic administration of streptomycin

The demonstration of the causative micro organism, P tularensis, in the sputum or pleural effusion is rarely possible by direct examination For this reason, it is advisable to inoculate the suspected specimen intra-peritoneally into mice and guinea pigs and prepare cultures from the scrapings of the spleen of the infected animal, on cystin agar medium Growth is recorded in four days Positive cultures are obtainable from such specimens in 60 to 70 per cent of the cases Similarly, confirmatory evidence of the disease can be demonstrated by cultures from the primary ulcer and from the blood Downs and her associates showed that P tularensis grew abundantly in the yolk sac of embryonated *chicken and duck egg*

Skin testing is a valuable early diagnostic aid Skin tests are positive prior to the appearance of clinically significant titers of agglutinins, provided the right materials and proper technique are used Intra

cutaneous injection of killed bacterial suspension of Foshay is positive in over 90 per cent of these patients Foshay s antiserum given in the same manner is bound to result in positive reaction in 100 per cent

No specific information can be derived from hematologic examinations Normal white blood cell count may coexist with tularemic pneumonia, but usually, there is an increase in the number of rod and S shaped polymorphonuclear leukocytes More often, one finds a mild or moderate leucocytosis, up to 20,000 per cubic millimeter At the same time, there is a predominance of lymphocytes In other instances, the number of neutrophylic leukocytes may rise to 80 85 per cent The sedimentation rate of the erythrocytes is accelerated as it is seen during the course of a great many other inflammatory diseases

Inasmuch as the symptoms, physical and x ray findings of this disease may closely resemble those of a number of other pathologic conditions, due consideration should be given to differential diagnosis One should rule out atypical (virus) pneumonia, tuberculosis, influenza, various forms of fungus disease of the lung, brucellosis, typhoid fever and paratyphoid, typhus and other bacterial, rickettsial, viral and parasitic infections which may be associated with bronchopneumonic or pneumonic consolidation, severe bronchitis and pleurisy with effusion For details concerning these items the reader is referred to the respective chapters

Prognosis

Prior to the introduction of streptomycin in clinical practice, the prognosis was grave in tularemic pneumonia The mortality rate, as recorded in large groups of patients, varied from 30 to 50 per cent Without treatment with streptomycin or aureomycin the febrile period lasted from two to four weeks and in some cases, complete recovery took months or even years Dyspnea persisted in some of these patients even after apparent recovery, due to extensive residual peribronchial fibrosis The latter, according to the observations of Blackford and Casey (1941), may remain visible in the roentgenogram even in cases of tularemic bronchitis without pneumonia

One of the peculiarities of tularemic pneumonia is that its healing is slow even with adequate doses of streptomycin, although it is accelerated by this drug as compared with cases treated without streptomycin Also, it is interesting that despite this specific treatment, permanent pulmonary fibrosis may follow the acute phase Not unlike the pneumonic

process, pleurisy with effusion caused by *P tularensis* disappears only slowly even on adequate treatment with streptomycin It was pointed out by Foshay and Pasternack (1946) that early streptomycin therapy does not jeopardize the immunologic status of the patient after recovery Immunity persists for a lifetime against exogenous infection They attribute the occasional occurrence of a second attack of tularemia in these individuals to a breakdown of the immunologic balance attained at the time of recovery Consequently, pathogenic micro organisms kept dormant or under control by forces of specific immunity are liberated

Treatment

Streptomycin and aureomycin are the specific remedies of this disease First, Heilman in 1944 demonstrated experimentally the sensitivity of P tularensis to streptomycin Clinically, it was introduced by Foshay and Pasternack with good results Hunt in 1947 first administered streptomycin for the treatment of pleuropulmonary tularemia The therapeutic response to this drug is dramatic Toxic symptoms disappear rapidly and great improvement is noticeable in the status of the patient Complete recovery can be expected from the administration of 0 5 gm of streptomycin daily for a period of six days The drug is given intramuscularly in a single dose each day To dangerously ill patients, it should be administered by the continuous intravenous drip method

In case of delay in confirmatory laboratory proof of the diagnosis, it is justifiable to administer streptomycin on the basis of a presumptive diagnosis, provided other diseases are ruled out with reasonable certainty Allergic skin manifestations incidental to streptomycin injections such as urticaria with or without pruritis or papulomacular erythema, can be effectively checked by benadryl or pyribenzamine, 50 mg three times a day, or by other useful antihistaminic preparations

In spite of the excellent results that can be anticipated with the use of streptomycin, certain supportive and symptomatic therapeutic measures may be found expedient In this regard, oxygen inhalation in the management of severe dyspnea, medicinal relief of intense cough or excruciating chest pain are of particular importance. Also, it is advisable to remove large pleural effusions by aspiration, repeatedly if necessary Smith and Atwell recommended intrapleural instillations of streptomycin, in addition to its intramuscular use

Aureomycin was first used in this disease by Woodward and his associates in 1949 This antibiotic is administered orally in doses of 0.5

gm every four hours for the average adult According to Parker and his associates, chloramphenicol is also beneficial when it is given in the same dosage after an initial dose of 2 to 3 5 gm

In a study of 44 cases Corwin and Stubbs found aureomycin as effective in securing remissions as streptomycin but its curative effects did not compare with those of other antibiotics These patients were successfully treated with streptomycin or dihydrostreptomycin in 6 gm in six days Rosenthal treated 54 patients aged from 6 months to 72 years, two died but in these therapy was started late Clinical response is rapid if started in the first week Satisfactory results have been obtained later but less dramatically

In view of the wide occurrence of this disease, it is well to call attention to its prophylaxis

(1) Individuals who are likely to handle infected animals or may be exposed to them by direct contact or through vectors, should wear rubber gloves and tick proof clothing, as occasion may require

(2) Only immune personnel should engage in laboratory work connected with potential risk of exposure to this micro organism

(3) Refrigeration does not kill P tularensis

(4) No raw drinking water should be consumed in areas where tularemia is common in wild animals

(5) Infected meat should be thoroughly cooked before eating

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ACUTE PNEUMONITIS

This subject is presented in connection with diseases of diverse origin in other parts of the book, particularly in sections on Primary Atypical Pneumonia, Influenza, Rheumatic Pneumonia, Ornithosis and Pulmonary Diseases Caused by Noxious Gases, Fumes and Dusts

ASPIRATION PNEUMONIA

The clinical aspects of this condition are discussed in sections on Bacterial Pneumonia, Lipoid Pneumonia, Diseases of the Oesophagus (Cardiospasm, Diverticulum, Carcinoma), Pulmonary Diseases Caused by Noxious Gases, Fumes and Dusts, Foreign Bodies in the Air and Food Passages

LIPOID PNEUMONIA

By ANDREW L BANYAI, M D AND J WINTHROP PEABODY, M D

(*Synonyms* *Lipid pneumonia, Fat pneumonia, Steatosis of the lung, Lipoid pneumonitis, Lipoid pulmonitis, Oil pneumonia, Oil aspiration pneumonia, Oil inspiration pneumonia Pneumolipoidosis, Pneumoliposis, Pulmonoliposis, Paraffinoma Pulmonary oil tumor, Paraffin oil tumor*)

Lipoid pneumonia is characterized by a foreign body type of inflammation of the lung which is associated with considerable fibrous tissue formation The disease is caused by the aspiration of mineral oil when taken as a laxative, or following the application of medicated oils and oily salves the base of which is liquid petrolatum, when these are used for spraying the upper respiratory tract or applied in the nose, especially when this is done before retiring Lipoid pneumonia may also result from the aspiration of fish oils, milk, and cream The incidence of this condition is highest in infants, in children with constitutional debility, and in aged, weakened, bedridden individuals Faulty deglutition due to weakness or to inflammatory or neoplastic diseases of the mouth, pharynx, and esophagus, or caused by neurological disorders, is often responsible for the aspiration of oil However, it has been demonstrated experimentally that oil deposited in the nose at night may find its way to the lungs in healthy persons A number of instances of lipoid pneumonia have been reported in previously apparently normal individuals

Storrs and his associates reported a case of extensive lipoid grar loma of the lung, which developed as the result of a bronchogram wi iodized peanut oil after a two months interval The diagnosis was coi firmed by histologic examination after lobectomy Similar instance were recorded by Rabinowitch and Lederer, Wright and Brody Con sidering the universal use of iodized oil for bronchograms, the incidence of this complication is evidently extremely low

Proudfit and his associates reported a case due to a mineral oil spray used in cleaning and lubricating cash registers for 17 years

When animal or mineral oil reaches the lung, it induces capillary congestion, with consequent local edema The latter represents a predilectional place for the propagation of infectious micro-organisms and therefore favors the development of bronchopneumonia The aspirated oil droplets in the alveoli are phagocytosed by large mononuclear cells which fill the alveoli and cause consolidation The ingress and passage of these cells in the interstitial supportive tissue of the lungs and in the

lymphatics set up additional irritation which results in fibrous tissue proliferation Obstruction of the bronchioles by oil is followed by atelectasis and by possible infection and fibrosis of the corresponding area of the lung

Pulmonary disease caused by aspiration of oil is most commonly localized in the basal and perihilar regions However, scattered lesions involving extensive areas are also seen The posterior regions are pre dilectional sites The right lung is more often involved than the left Some of these cases may simulate caseous pneumonia, primary tuber culosis with bronchopneumonic or pneumonic involvement, early infil trate, or chronic fibroid tuberculosis lesions Lipoid pneumonia may be acute or chronic The local symptoms include persistent or recurrent cough which may be productive or unproductive, blood streaked sputum, sense of pressure or pain in the chest, and dyspnea when the lesion is extensive These symptoms as well as the constitutional mani festations are greatly influenced by the presence of complicating bronchitis, bronchiolitis, bronchopneumonia and bronchiectasis As a rule, the general symptoms are disproportionately slight Fever may be entirely absent, or recurrent low grade or moderate fever is noted The periodic febrile episodes (with possible associated night sweats) are closely related to repeated aspirations of oil, or to intercurrent pulmonary infections During the protracted course of the disease the patient may complain of malaise Endogenous lipoid pneumonia may develop in patients with chronic bronchial and bronchiolar obstruction associated with inflammation of low grade

The physical findings correspond to the location and extent of the lesion The percussion note is impaired or dull The breath sounds are harsh or bronchovesicular, in some instances they are diminished Fine moist rales are detected over the diseased lung The roentgenogram pre sents a varied picture In early cases, one finds an exaggeration of the bronchovascular markings In some instances x ray examination reveals a scattered nodular and linear fibrosis, in other cases a large area of homogeneous haziness can be visualized which extends from the hilum toward the periphery, and may have a sharply circumscribed or feathery outline Furthermore, the roentgenogram may show massive fibrosis of irregular or rounded form which is either centrally located or it is found mesially between the hilum and the diaphragm Complicating broncho-pneumonia is bound to obscure these findings

The differential diagnosis is not a simple matter Assuming that

pulmonary infection, neoplasm and infarction have been excluded with reasonable certainty, the history of using oils for an extended period of time offers a clue for further investigation Demonstration of free oil droplets in the sputum is not diagnostic but highly suggestive Also, oil droplets may be found in oil-laden macrophages (lipophages) in the sputum These cells are derived from the lining cells of blood vessels, lymph vessels and alveoli Occasionally, when the cellular nucleus is pushed to the periphery the cells give the impression of a signet ring Cod liver oil is identified by the following tinctorial characteristics It stains red with sudan IV, blue with nile blue sulphate, black with osmic acid, and reddish purple with Ziehl-Neelsen Mineral oil stains yellow orange with sudan IV, pink with nile blue sulphate, it does not stain with osmic acid or with Ziehl Neelsen Bronchoscopic aspiration may secure oil laden phagocytes when no satisfactory sputum is available Also, if necessary a biopsy specimen can be taken from the vicinity of the lesion with the aid of the bronchoscope, which may be instrumental in establishing the diagnosis

Treatment

In localized lesions, particularly when suppuration or bronchiectasis complicates the clinical picture, segmental resection or lobectomy is indicated Otherwise, one should resort to supportive and symptomatic measures Antibiotics are used in case of secondary infection The use of oils should be discontinued

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CHRONIC NONSPECIFIC SUPPURATIVE PNEUMONITIS

By Andrew L Banyai, M D and J Winthrop Peabody, M D

The term, chronic nonspecific suppurative pneumonitis, was introduced by Kerschner and Adams for the designation of a condition with the following pathologic characteristics Grossly, the lung involvement occupies one or two lobes The diseased area is dense and firm in consistency Microscopically, there are extensive interlobular and interalveolar fibrosis, thickening of the alveolar walls, lymphoid and plasma cell hyperplasia, redundance of the bronchial mucosa with consequent narrowing of the lumen, chronic atelectasis, exudate and blood in the alveoli

The onset is insidious and is not related to any acute disease of the lower air passages The course of this condition is a protracted one It may be of several years duration Significant symptoms are Cough expectoration and pulmonary hemorrhage Chest pain and moderate elevation of the temperature were observed in about 50 per cent of the cases

Physical examination reveals findings compatible with consolidation in one or two lobes Roentgenograms of the chest show diffuse, dense shadows in the corresponding areas of the lung Micro organisms are found on bacteriologic examination of the sputum aspirated bronchoscopic specimen and post operative material

Chronic nonspecific suppurative pneumonitis should be differentiated from lung abscess, bronchiectasis lipoid pneumonia, infarction benign and malignant tumors of the lung mediastinum pleura and diaphragm, tuberculosis and other lung infections

Antibiotics may bring about transient, symptomatic improvement According to Kershner and Adams, the treatment of choice is lobectomy Nicholson stated that once suppuration had occurred, resection of the affected lobe or lung is the only measure likely to restore the patient to health

Waddell and his associates and Robbins and Sniffen described a similar clinical entity called chronic pneumonitis of the cholesterol type The most remarkable feature of the condition reported by them is the bright yellow color of the involved areas of the lung during the early phase of the disease The yellow coloration of the lung tissue is caused by the deposition of large amounts of cholesterol and cholesterol esters The concentration of cholesterol and its esters in the

diseased regions may be 90 times normal values Tuberculosis, bronchiectasis, lung abscess were ruled out as possible incentive factors in the accumulation of cholesterol In the chronic phase of the disease, the yellow color of the lung tissue becomes less intense and it is restricted to smaller areas It is supplanted by gray fibrous tissue

According to Robbins and Sniffen, the onset was sudden in more than half of their cases The symptoms were cough, expectoration of white, mucoid or brownish sputum, chest pain and fever Frank pulmonary hemorrhage has also been observed Roentgenologically, the lesion is occupying the entire extent of one lobe or only one or more segments

Differential diagnostic and therapeutic considerations relative to pneumonitics of the cholesterol type are the same as apply to chronic nonspecific suppurative pneumonitis

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CHEMICAL PNEUMONIA

Pertinent information on this subject is presented in the sections on Pulmonary Diseases Caused by Noxious Gases, Fumes and Dusts, Pneumopathies Resulting from Conflagration

TRAUMATIC PNEUMONIA

Traumatic pneumonia is discussed in the section on Acute Thoracic Injuries

HYPOSTATIC PNEUMONIA

This condition is discussed in sections on Pulmonary Edema and Bacterial Pneumonia

CHRONIC FIBROID PNEUMONIA

(Synonyms Indurative pneumonia, Cirrhosis of the lung, Fibroid lung, Chronic pneumonitis)

A detailed discussion of this subject is presented in the section on Pulmonary Fibrosis

LOEFFLER'S SYNDROME

By Andrew L Banyai, M D and J Winthrop Peabody, M D

This disease entity is named after Loeffler, Professor of Medicine at the University of Zurich, Switzerland who first reported his pertinent observations on the subject in 1932 It is characterized by transitory, migratory x ray shadows in the lung associated with eosinophilia in the peripheral blood and with absent or low grade constitutional symptoms

It is the consensus that the clinical manifestations of Loeffler's syndrome are due to allergy which causes an increased vascular permeability in the lung A number of concepts have been proposed relative to the essential pathologic changes before occasion arose for post mortem studies Loeffler, in 1932, 1936, assumed that there was an inflammatory exudate similar to that in erythema nodosum Engel and Blanton expressed the view that localized pulmonary edema was the essential feature of the disease Soderling was of the opinion that pathologic alterations in the lung resulted from bronchiolar spasm and exudation in the small bronchi, with consequent localized atelectasis Gravesen attributed them to reactions in the interstitial tissue as a shock organ in contrast to bronchial reactions seen in ordinary asthma

The pathologic substrate of Loeffler s syndrome was first revealed in the report of Meyenburg in 1942 He made necropsy examinations on four persons with this disease, three of whom died in accidents and one from tetanus The lung lesions were represented by dense, airless foci of bronchopnumonia or lobar pneumonia There was exudation in the alveoli and in the interstitial tissues In two of the cases also evidence of bronchitis and bronchiolitis was noted Cytologic examination revealed large numbers of eosinophiles in the blood, bone marrow and various organs Over areas of pulmonary involvement, the pleura showed inflammatory changes Bayley and his associates reported necropsy findings in a woman aged 59 years Irregular areas of increased consistency, varying from a few millimeters to 5 cm in size were scattered throughout both lungs The nodular sites resembled tubercles Histologic examination of organized pneumonia revealed numerous fibroblasts, collagenous fibers, plasma cells, lymphocytes and an unusually large number of eosinophilic leukocytes and some giant cells Within the pneumonic lesion, tubercle-like formations were seen which consisted of acidophilic, granular necrotic center with mononuclear cells, fibroblasts and occasional giant cells surrounded by histiocytes, epithelioid cells and fibroblasts, the periphery

being made up of eosinophilic leucocytes, plasma cells and lymphocytes They call attention to the superficial resemblance of the nodular, granulomatous changes encountered in rheumatic fever This points toward the possible common mechanics of pathogenesis of these two conditions namely hypersensitiveness Other findings of interest include periarterial and pericapillary inflammatory process with eosinophilic leucocytes and plasma cells predominating, changes characteristic of interstitial pneumonitis with thickening of the interalveolar septums Areas with more recent inflammatory lesions showed the alveoli filled with the same cellular elements in addition to serum, fibrin and red blood cells They observed that the bronchial lesions were the same as in bronchial asthma "Hypertrophy of the muscle of the bronchial wall was not pronounced but the predominantly eosinophilic exudate infiltrating all portions of the wall the marked hyalinization and thickening of the basement membrane of the epithelium and the presence of large quantities of mucus in the cells and lumens were all typical of bronchial asthma "

Harkavy on the basis of his observations in patients with migratory pulmonary lesions advanced the concept that the roentgenologically demonstrable changes were attributable to a hyperergic reaction on the part of the interalveolar capillaries and the larger blood vessels of the lung which become shock organs to certain allergens Vascular response in such cases varies from thickening and eosinophilic cell infiltration of the wall to manifestations typical of periarteritis nodosa, depending upon the intensity and duration of the angiotropic allergic reaction It is assumed that in typical cases of Loeffler s syndrome, reversible vascular changes take place These are associated with increased permeability localized edema and predominantly eosinophilic cellular accumulations in the alveoli bronchial wall and interstitial tissue of the lung In one of his cases Harkavy demonstrated thickening of the walls of small pulmonary vessels Bayley and his associates found extensive vascular lesions which consisted of hypertrophy of the media and thickening of the intima of arterioles and the small and medium sized arteries Consequently, the lumens of these channels were reduced Also, they observed evidence of necrotizing arteritis and arteriolitis which closely resembled histologic findings in periarteritis nodosa

It is important from the etiologic point of view to recognize two main groups of cases with Loeffler s syndrome In the first group its cause is identified, while in the second group, the causative agent remains obscure throughout the course of the disease In other words, Loeffler s syndrome

comprises a number of diseases of heterogenous etiology Evanescent pulmonary infiltrations with eosinophilia in the peripheral blood have been observed in the following conditions

(1) Ascariasis
(2) Infestation with Taenia saginata
(3) Amebiasis
(4) Trichinosis
(5) Strongyloidosis
(6) Infestation with Fasciola hepatica (Distoma hepaticum)
(7) Infestation with Trichuris trichiura
(8) Hookworm disease (infestation with Necator americanus, uncinariasis, ancylostomiasis)
(9) Helminthiasis of the skin due to Ancylostoma brasiliense
(10) Coccidioidomycosis
(11) Tuberculosis
(12) Inhalation of the pollen of Ligustrum or other allergens
(13) Bacterial allergy
(14) Sensitization to drugs, such as sulfonamides penicillin in oil and wax gold and para aminosalicylic acid
(15) Overexposure to ultraviolet rays
(16) Cave sickness

The role of hypersensitiveness in the pathogenesis of Loeffler s syndrome has been confirmed by recent experimental investigations Herbut and Kinsey succeeded in reproducing this condition in sensitized rabbits by giving single or repeated intratracheal instillations of horse serum In this manner, they were able to demonstrate roentgenologically transitory shadows in the lung which disappeared in from 7 to 13 days Other relevant findings were eosinophilic leucocytes in the tracheal secretions, congestion, edema, eosinophilic infiltration of the submucosa of the trachea and bronchi parenchymal congestion, edema, atelectasis, eosinophilic pneumonia and emphysema

As a confirmation of the allergic origin of clinical cases of Loeffler's syndrome, Blanton recorded that in his patient roentgenologically visualized pulmonary infiltrations disappeared after the subcutaneous injection of 0.5 cc of epinephrine

One of the cardinal features of this condition is the fleeting nature of the lung lesion According to the original observations and our own experience, it disappears in from three to eight days For this reason, appropriately, it has been referred to as transient, transitory, evanescent,

shifting, fugitive or fugacious infiltration During recent years, three other variants of this disease have been recognized Smith and Alexander, Loehr, Leon Kindberg and his associates, Karan and Singer, Serra and Ham and Zimdahl reported transitory pulmonary eosinophilic infiltrations with severe, acute onset and with subsequent disease of several months duration Another form of eosinophilic infiltration of the lung was described by Schulze, Kartagener and also by Ham and Zimdahl In these cases the disease was characterized by an onset with mild symptoms and by a chronic course of several months to more than one year s duration and by fluctuations in the symptoms and the associated eosinophilia Harkavy is given credit for describing a group of patients with Loeffler s syndrome all but one of whom had bronchial asthma Presumably the disease which ran a protracted course was due to hypersensitiveness to bacterial proteins *With one exception*, all of his patients in this group had eosinophilic polyserositis

Symptomology

It is a matter of record that in a substantial number of instances the disease has been discovered on routine x ray examination of the chest In other cases, prodromal symptoms occur, such as anorexia, headache malaise and night sweats These are followed by grippe like aching weakness and possibly by loss of weight In the majority of patients, fever is absent When it is present, it is usually low In rare instances it may reach 104° F (40 0° C) and is preceded by chilliness and followed by drenching sweating, with return of the temperature to normal the next day As a rule subjective signs of toxemia are vague

Patients who seek medical attention usually complain of mild, moderate or severe irritative periodically recurring cough The latter is either dry and hacking or it is productive of small amounts of scant, frothy, mucoid or mucopurulent sputum At times, the sputum has a metallic taste Rarely palpitation may be complained of and also dyspnea in extensive bilateral lesions A few cases have been reported with minor pulmonary hemorrhages In a number of cases concurrent bronchial asthma or bronchitis has been noted Infrequently, soreness or stabbing pain in the chest is present

Diagnosis

Loeffler s syndrome occurs at all ages and in all races It is more frequent in males than in females Its incidence is high in the spring and summer months, with a peak in July and August Inquiry in the personal

and family history is of importance It may reveal asthma, hay fever, vasomotor rhinitis, urticaria, eczema, angioneurotic edema, migraine or other manifestations of allergy Some patients develop these conditions after their recovery from Loeffler s syndrome

The most striking feature of the disease is the marked discrepancy between symptoms and physical findings on one hand and x ray changes on the other In the presence of extensive opacities in the lung field, symptoms may be entirely absent Simultaneously, one may find no deviation from normal on physical examination In other instances, there are slight impairment or dullness of the percussion note, harsh breath sounds, or bronchovesicular breathing, inconstant moist rales or crepitations over circumscribed areas of the chest or widely distributed sonorous and sibilant rales Friction sound is rarely found In rare instances signs of pleural effusion are detectable Cyanosis of the lips and fingers is observed only in patients with very extensive pulmonary involvement

The x ray appearance of the lung lesion shows a multiplicity of forms, extent and density in various individuals As a matter of fact, it is one of the chief characteristics of the disease that roentgen shadows may run a gamut of changes in the same individual during the course of the disease They may be of homogeneous or uneven density, fleecy or heavy round triangular or of bizarre irregular shape, nodular miliary or patchy Their margins are ill defined or confluent The opacity may occupy the extent of one lobe or the entire area of one lung The lesions are either unilateral or bilateral asymmetrical or symmetrical Their location may be basal, perihilar or in the upper one half of the lung The involvement may appear in the form of a radiating shadow extending from the hilum toward the periphery One of the characteristic aspects of Loeffler s syndrome is the rapid evolution and disappearance of x ray shadows It is amazing indeed to see complete clearing of what seem to be large areas of consolidation within a few days Subsequently similar opacities may be discovered in other segments of the lung or they may reappear at their previous location It is obvious that for the sake of accurate diagnosis, it is mandatory to take serial roentgenograms of the chest at short intervals preferably every few days or once a week As a rule, no residual fibrosis remains after recovery Contrary to this observation Harkavy noted organized productive infiltrations in the central lung fields of one of his patients Also, Bayley and his associates reported the occurrence of advanced organization of the pneumonic exudate on post mortem examination In rare instances findings typical of pleural effusion

are noted in addition to the parenchymal involvement *Thoracocentesis* reveals a clear, transparent, straw-colored or sanguineous fluid It contains from 60 to 95 per cent eosinophilic leucocytes, large amounts of fibrin and Charcot-Leyden crystals

Freund and Samuelson observed in their patient a firm, tender supra clavicular lymph node the size of a plum at the same time that x ray examination revealed the lung lesion The enlargement of the lymph node disappeared in nine days, with simultaneous marked clearing of the lung In one of Harkavy's cases generalized lymphadenitis developed Biopsy of a lymph node showed heavy eosinophilic infiltration Also, Harkavy pointed out that pulmonary manifestations of Loeffler's syn drome may be but one of the expressions of a general vascular allergy The latter may lead concurrently or alternately to pathologic changes in other organs and tissues under the effect of the same allergenic stimulation If this is the case, it is reasonable to assume the possibility of coincidental or subsequent periarteritis nodosa The latter was identified on biopsy of the skin and muscle in one of his patients Reference has been made to the occurrence of eosinophilic pleurisy, pericarditis and peritonitis in some of his patients Furthermore, he recorded other complications, such as purpura and necrosis of the skin, both with perivascular eosinophilic infiltration on biopsy, polyneuritis and transient polyarthritis Electrocardiographic examination revealed abnormalities in the deflections and in the amplitudes of P waves, T waves and Q R S complexes At the same time, enlargement of either one or both ventricles was noted Harkavy states that these findings disappeared with the recession of pul monary changes and other allergic manifestations In one of his cases, post mortem examination showed hyperergic vascular changes in the coronary vessels and in the pericardium, progressing to the stage of peri arteritis nodosa In his opinion, the reversibility or irreversibility of elec trocardiographic signs was predicated upon the degree of hypersensitive ness, the extent and duration of vascular reaction and injury to the myocardium resulting from ischemia

Eosinophilia in the peripheral blood is a cardinal feature of Loeffler s syndrome It varies from 10 to 70 per cent Increase in the number of eosinophilic leucocytes usually ensues simultaneously with the pulmonary changes In cases with fever, there may be a lag of a week or so in the development of eosinophilia The latter is bound to be fluctuating and is not proportionate to the extent of the pulmonary lesion After it reaches its peak then the infiltration in the lung begins to disappear Stahel in

1938 and others made bone marrow biopsies and found that there was a stimulation of bone marrow function, with consequent increase in the eosinophilic leucocytes

Other pertinent laboratory findings include slight or moderate leucocytosis and a somewhat accelerated sedimentation rate of the red blood cells Rarely, one finds leucocytosis as high as 30,000 per cubic millimeter The sputum may show the presence of a large number of eosinophilic leucocytes

Differential Diagnosis

The polymorph roentgenologic findings in Loeffler s syndrome require the consideration of a long list of diseases so as to arrive at a correct diagnosis These are

Tuberculosis
Bronchopneumonia and pneumonia caused by bacterial rickettsial or viral agents
Sarcoidosis
Rheumatic fever
Atelectasis
Pulmonary congestion
Pulmonary edema
Infarction
Primary and metastatic tumors of the lung and mediastinum
Diseases of the hemopoietic system associated with eosinophilia
Eosinophilic leucocytosis
Paragonimiasis
Schistosomiasis
Clonorchiasis
Tropical eosinophilia (Pulmonary eosinophilosis)
Pulmonary acariasis
Cave sickness
Pulmonary conditions with nodular x ray shadows See outline in chapter on Lupus Erythematosus
Pulmonary diseases associated with round shadows on the roentgenogram These are enumerated in the chapter on Pulmonary Adenomatosis
Pleural effusions with high percentage of eosinophilic leucocytes These include tuberculosis, rheumatic fever, cardiac decompensation, neoplastic involvement of the pleura, hemorrhagic effusions resulting from trauma, tumor or pulmonary infarction

Prognosis

Loeffler s syndrome is a benign disease in the overwhelming majority of cases On the basis of incidental detection of this condition in persons who have no symptoms referable to the respiratory tract, it is likely that there are innumerable instances where the disease runs an asymptomatic, latent course with spontaneous recovery Even in frank clinical cases, the disease is characterized by a brief, uneventful course All symptoms signs and x ray findings are likely to disappear in from a few days to a few weeks Rarely, the complete disappearance of the roentgenologically demonstrable lung lesion may take months Recurrences in the same lung or on the contralateral side have been observed In such instances the duration of the disease may extend from one to four years Although in a great many instances Loeffler s syndrome is self limited, its course can be substantially shortened by specific medical treatment So far only a few fatal cases have been recorded

Treatment

Specific medicinal measures are at our disposal for the treatment of this condition when it is caused by parasitic infestation Attempts at hyposensitization are mandatory when hypersensitiveness to plant or animal allergens or to bacterial proteins is the cause of the disease. Symptomatic and supportive measures are called for in long standing disease, according to requirements of the individual case For the treatment of associated bronchial asthma the reader is referred to the respective chapters, *Asthma in Adults* and *Asthma in Children* In rare cases of severe dyspnea, inhalation of oxygen and helium under positive pressure or inhalation of a mixture of 5 per cent carbon dioxide and 95 per cent oxygen may bring about satisfactory relief Ham and Zimdahl used theophylline with ethylenediamine, 7½ grains (0 5 gm) given intravenously in 20 cc of water, with success for the same purpose In some instances pituitary adrenocorticotropic hormone (ACTH) may bring about prompt disappearance of the pulmonary infiltration ACTH is administered intramuscularly in doses of 25 mg every six hours for two days Subsequently, it may be necessary to continue the treatment with doses of 5 mg

Regall and McGinnis reported excellent results in treatment of a case with ACTH Vines and Clark also noted dramatic improvement after ACTH therapy Westwood and Levin prepared a good review of the literature on the eosinophilic lung

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RADIATION PLEUROPNEUMONITIS

By Andrew L Banyai, M D and J Winthrop Peabody, M D

X-ray therapy is a well established method in the management of carcinoma of the breast, as well as in the treatment of malignant neoplasms of the esophagus mediastinum and certain cases of inoperable cancer of the lung Possible deleterious effect of radiation energy upon the lung tissue has been anticipated since the early days of x-ray treatment Wohlauer's experiments in 1909 showed the development of congestion in the lungs of guinea pigs from [illegible] irradiation With [illegible] rabbits by x ray irradiation [illegible] gstad in 1934 produced [illegible] The course of pathologic changes consisted of four stages

(1) The earliest alteration began from one to two hours after irradiation There were degeneration of the lymph follicles, hyperemia, pronounced increase in the bronchial secretions, transudation and moderate leucocytic infiltration

(2) The subsequent latent period lasted from [illegible]

(3) The main react[illegible] its maximum from [illegible] characterized by pro[illegible] pouring of leucocytes followed by the [illegible] This phase is appearance of macrophages and giant cells

(4) The final stage consists of proliferation of connective tissue sclerosis and slight proliferation of bronchial epithelium In one-half of the experimental animals, more or less widespread calcification was noted in the lung in the form of small disseminated particles similar to that found in human beings with mitral stenosis

Tyler and Blackman (1922) are credited as being the first to report on pathologic changes in the lung of patients who received x-ray therapy Since then, Grover and his fellow workers (1923) and several other clinicians corroborated these observations Weatherwax and Robb proved experimentally by phantom measurements that x-ray irradiation of the chest given with cross fire technique through two portals at right angles is capable of producing an intensity of radiation at 10 cm depth in the lung, which equals the surface dose of x-ray Widman (1941) calculated that treatment with from 1,600 to 2,000 r applied to the chest in fractioned doses through three or four portals at a rate of three treatments

a week delivered a lung dose which was sufficient to cause pathologic pulmonary changes in some of the patients

The clinical evidence of radiation pleuropulmonitis shows great variations Hansen noted it in 4 6 per cent of his cases, while Widman reports 22 6 per cent Engelstad observed its occurrence in 5 4 per cent of patients with breast cancer and in 20 4 per cent of those with carcinoma of the esophagus who were given x-ray therapy Abnormal findings were seen by McIntosh in roentgenograms of 60 per cent of patients treated with x-ray

Also, there is great divergence in the post mortem incidence of this condition Dawns found it in less than 1 per cent and Warren and Spencer in 12 per cent A good perspective of the situation can be gained from the tabulated data recorded by Leach and his collaborators (1942) Of 347 patients with operable breast cancer who were treated with x ray, they found roentgenologic evidence of radiation disease of the lung in 22 1 per cent

METHOD OF TREATMENT	NUMBER OF PATIENTS	PULMONARY CHANGES DUE TO IRRADIATION	
		Number	Percent
(1) Preoperative			
(A) Massive doses 500 700 r per portal	11	1	9 0
(B) Divided doses 300X6 per portal	57	31	54 0
(C) Radium element pack 8 000X3 mg hour per portal	31	2	6 0
(2) Postoperative			
(A) Massive doses	77	7	9 0
(B) Divided doses	41	8	19 0
(C) Radium element pack	7	0	0 0
(3) Pre and postoperative			
(A) Massive doses	37	8	21 0
(B) Divided doses	3	1	33 3
(4) Miscellaneous			
(A) Massive doses, interstitial radium surgery	40	3	7 5
(B) Divided doses interstitial radium, surgery	19	8	42 0
(C) Interstitial radium, surgery	8	1	15 0
(5) X ray irradiation only	16	7	43 7

It is the consensus that larger quantities of radiation energy are more likely to produce pathologic changes in the lung than smaller ones Even so, neither objective findings nor symptoms are necessarily proportionate to the intensity of irradiation It is evident, therefore, that radiation energy is not the only determinant of the clinical manifestations of this condition Great differences in the rapidity of development and extent are brought about by such factors as the age of the patient, presence or absence of arteriosclerosis and pulmonary metastasis or infection, also, possible variations in individual tissue sensitivity to radiation McIntosh expressed the view that advanced age and arteriosclerosis favored the development of radiation fibrosis of the lung Moreover, she observed that very large portals, such as 20 × 20 cm, are bound to increase the tendency to pulmonary damage on account of the larger volume irradiated Cross firing into the mediastinum is likely to produce greater pulmonary changes than similar radiation energy given into the peripheral lung These data are presented with the qualification that there are a number of instances of severe pleuropulmonitis in persons in their thirties even though the intensity of x-ray treatment was not excessive Some clinicians seriously question the predisposing influence of coexisting pulmonary infection or metastic spread in the lung

Advanced changes in the lung induced by radiation energy consist of massive fibrosis Areas of varying extent become transformed into sclerotic tissues Through its inherent tendency to contraction, fibrosis is bound to reduce the size of the lung so that in severe cases, it may not be larger than a man s fist Excessive contraction of the lung implies a profound effect upon the topographic relationship of adjacent organs and structures The heart, large thoracic vessels and other mediastinal structures are displaced toward the affected side The corresponding hemidiaphragm is shifted upward and the entire hemithorax is decreased in size The intercostal spaces are narrowed and there is an increased slanting of the ribs on the diseased side

An excellent description of the histologic findings is given by Warren and Spencer which is based on the post mortem examination of 29 cases The earliest detectable injury is to the alveolar lining cells and to the capillary endothelium This is associated with edema, swelling, necrosis and proliferation of these cells There is a hyaline membrane closely adherent to the alveolar walls In addition, one may note one or all of the following changes Swollen alveolar lining cells with or without desquamation, unusual fibrillar hyalinization of the alveolar walls with

pronounced thickening, edema of the interstitial tissues, hyalinization of the arterial walls, interalveolar capillary thrombosis, peribronchial and perivascular fibrosis There is a definite evidence of bronchitis, attributable to radiation energy Atelectasis is common in areas adjacent to heavy pulmonary fibrosis Also, bronchiectasis may be noted, although it is not a constant corollary of this condition Dilation of the blood vessels of the bronchial mucosa is often seen Their appearance is not unlike telangiectasis which develops in the skin after repeated irradiations Acute consolidation is rare During the chronic phase of the disease, complications may be observed in the form of superimposed infections

Involvement of the pleura is virtually always present in these cases On post mortem examination, the pleura is found to be markedly thickened by fibrosis Sometimes, it is almost as hard as cartilage Adhesions between visceral and parietal pleurae are common Adhesions at the base of the lung may be observed even when radiation is directed to the upper one half of the lung Pleuropericardial adhesions are frequent Occasionally, pleural effusion develops The latter, rarely, is localized in the interlobar region Pericardial effusion may complicate the picture

It is reasonable to anticipate cor pulmonale in patients with extensive radiation pleuropulmonitis It was present in 75 per cent of the cases of Fried and Goldberg as recorded on post mortem examination Cor pulmonale is brought about by the interplay of several factors These are

(1) Extensive loss of respiratory surface area due to the obliteration of alveoli by fibrosis, atelectasis or metastatic carcinoma

(2) Interference with free air flow by constricting peribronchial and peribronchiolar fibrosis

(3) Obstruction of normal blood circulation in the pulmonary vessels by perivascular fibrosis

(4) Pulmonary vascular fibrosis

(5) Mediastinal fibrosis which causes a partial constriction of large branches of the pulmonary vein

(6) Dislocation of the heart toward the affected side, assuming that it is associated with a kinking of the pulmonary vein or otherwise interferes with normal cardiac function

Symptomatology

Reference has been made to the incongruity between the extent of radiation disease of the lung and concurrent symptoms The latter may make their appearance prior to roentgenologically demonstrable lung

changes On the other hand, several months, sometimes a year and a half may pass before respiratory symptoms develop There are instances where, in spite of abnormal findings in the x ray film, complaints are entirely absent Thirty per cent of the patients seen by McIntosh and Spitz belong to this category Symptoms with an early onset may persist for several months and then disappear

As a rule, cough is the earliest symptom At first it is slight, hacking unproductive The patient may complain of a chest cold that hangs on With the progression of the disease, cough may become slightly productive, quite severe and annoying Dyspnea is bound to intensify coughing for the reason that the irritability of the receptors of the pulmonary sensory nerves is increased in dyspneic individuals Pulmonary hemorrhage may occur The amount of expectorated blood varies from blood streaked sputum to frank, occasionally, massive hemorrhage The amount of the latter may be as much as one quart Both slight and massive hemorrhage may be recurrent They are attributable to the pronounced dilation of the blood vessels of the bronchial mucous membrane Tightness and pain in the chest are caused by involvement of the pleura and by dislocation of some of the thoracic viscera Dyspnea results from cardiorespiratory insufficiency brought about by the following factors

(1) Loss of respiratory surface area

(2) Reflex spasm of the peribronchial and peribronchiolar smooth muscles It is induced by the development of pulmonary fibrosis The existence of reflex bronchial and bronchiolar spasm explains why, in some instances, dyspnea is unproportionately greater than would correspond to the concurrent pulmonary fibrosis Also, the recognition of reflex bronchial and bronchiolar spasm solves the problem of variable degrees of dyspnea in persons with pulmonary fibrosis of about the same extent The difference in the severity of dyspnea is due to the differing degrees of susceptibility of the pulmonary smooth muscles to irritation caused by fibrosis

(3) Peribronchial fibrosis is likely to interfere with the normal ingress and egress of air

(4) Constriction of the pulmonary vascular lumen by fibrosis represents considerable obstacle to free blood circulation

(5) Extensive pleural thickening causes pronounced rigidity of the lung surface, which interferes with its functional competence

(6) Adhesions of great extent exert the same influence on pulmonary function

(7) Extensive pleuropericardial adhesions may have the same significance from the functional standpoint

(8) Pericardial effusion is a rare but possible factor in this respect

(9) Upward displacement and fixation of the hemidiaphragm in its elevated position deprives one lung of 35 per cent of its functional mechanism

(10) The aforementioned factors which are responsible for cor pulmonale

Dyspnea caused by radiation disease of the lung develops more rapidly in the aged than in younger individuals This clinical phenomenon is readily understandable when one takes into consideration certain anatomic and physiologic changes characteristic of senescence

(1) The lung tissue in the aged undergoes degenerative changes similar to those in the skin The number of elastic fibers is diminished Consequently, the lung becomes less expansile and less contractile With the decrease in pulmonary elasticity, there is a proportionate loss of the reserve functional capacity of the lung

(2) There develops in aged persons a gradual atrophy of the inspiratory and expiratory muscles This, in turn, leads to lessened respiratory motion of the thorax, with corresponding diminution of pulmonary ventilation

(3) In senescence there is ossification of the costosternal cartilaginous connections This rigidity adds to the lessened inspiratory motion of the anterior chest wall

(4) The flabbiness and weakness of the anterior abdominal wall are other potent factors in bringing about rapid dyspnea in the aged Weakening in the anterior abdominal wall is associated with ptosis of some of the abdominal organs The consequent lower position of the diaphragm interferes with its normal excursions, and thus with normal respiratory function

(5) To these items one should add a factor pointed out by Leach and his collaborators, namely, increased irritability of the inspiratory and expiratory reflex of Hering and Brauer They assert that this is brought about by pulmonary fibrosis Increased irritability of the Hering Brauer reflex receptors in turn, causes hyperventilation, blowing off excess carbon dioxide and thus induces dyspnea

Constitutional symptoms may or may not be present These are Unexplained fatigue, malaise, palpitation, occasional slight, transient fever and sweating

Local, as well as constitutional symptoms are aggravated by progression of the radiation fibrosis spread of metastatic carcinoma super imposed infection, bronchiectasis and cor pulmonale

Diagnosis

History of exposure to radiation energy, therapeutic, professional or otherwise sufficient to cause pathologic changes in the lung is a pre requisite In the early stage of the disease, physical findings are entirely negative In patients with an advanced lesion, the hemithorax is decreased in size and its respiratory motions are restricted Dull percussion note and absent or diminished breath sounds occasionally, a few fine moist rales are found on the affected side At the same time signs of emphysema are detectable over uninvolved areas of the same lung and over the opposite side The skin of the affected hemithorax may show signs of atrophy, teleangiectasis and pronounced, occasionally, stony hard induration

Roentgenologic findings differ according to the stage of the disease Pulmonary changes may be noted as early as one month after irradiation or their first appearance may become noticeable only one year after the first treatment The earliest x ray manifestation is a veil like haziness over the irradiated region This usually, disappears in one to two months In other instances, pathologic alterations in the roentgenogram may increase for three to four months and disappear in about six to nine months Warren and Spencer (1940) observed increased radiotrans lucency as the first finding In our opinion this peculiarity is most likely due to compensatory emphysema similar to that seen in association with generalized miliary tuberculosis of the lung These transient changes may be followed by irreversible evidence of lung damage The latter is char actrized by sharply demarcated strand like shadows radiating from the hilum toward the periphery Also there are irregular, dense, patchy opacities of segmental or lobar distribution In some cases virtually the entire area of one lung is covered by a homogenous dense shadow Occasionally calcified plaques are seen in the lung

With well developed heavy pulmonary fibrosis, one finds unmistak able signs of contraction of the diseased lung The involved hemithorax is decreased in size there is a greater declivity of the ribs than on the opposite side, with narrowing of the intercostal spaces The heart and other mediastinal structures are pulled toward the side of fibrosis The corresponding hemidiaphragm is elevated The respiratory excursions of

the latter as well as of the entire hemithorax are limited or absent. There is evidence of emphysema in the opposite lung and in the uninvolved parts of the diseased lung Sudden increase in the number and extent of patchy opacities speaks in favor of spreading metastatic carcinoma *It is well to bear in mind when interpreting chest roentgeno*grams of women who have had mastectomy that the x ray translucency of the chest is greater on the operated side than on the nonoperated side

It has been pointed out that involvement of the pleura is part and parcel of radiation disease of the chest Thickening of the pleura over the irradiated area of the lung contributes to the veil like appearance seen on the affected side Other manifestations of pleural changes are Blurred outline or tenting of the corresponding hemidiaphragm evidence of pleural thickening or occasional effusion in the area of interlobar fissures or elsewhere pleuropericardial adhesions and the presence of calcified plaques in the pleura

In long stand ng cases one may find evidence of eburnation of r bs with consequent irregular contour and also osteoporosis Fracture of some of these ribs or the clavicle on the same side may occur without known trauma Such an event may be followed by nonunion and pseudoarthrosis of the bone affected

Roentgenologic findings may closely resemble changes found in a number of other conditions These include the following

(1) Metastatic carcinoma with parenchymal distribution or with extension along the bronchi and blood vessels

(2) Organizing pneumonia and bronchopneumonia

(3) Pulmonary congestion and edema due to cardiac failure with or without consequent fibrosis

(4) Chemical pneumonitis and its sequels with or without associated fibrosis caused by noxious fumes and gases

(5) Silicosis asbestosis and other types of pneumonoconiosis Tremolite silicatosis is accompanied by pleural plaque formation

(6) Lipoid pneumonia The latter is more common in the aged than generally realized

(7) Atelectasis of segmental distribution which presents an irregularly outlined patchy shadow or shadows It may be caused by neoplastic or inflammatory changes or by aspirated foreign body

(8) Lung abscess with perifocal inflammatory changes and subsequent fibrosis

(9) Infarction which may be found in the form of a homogenous

patchy shadow of irregular outlines instead of the textbook picture of a triangular opacity with its base at the periphery and its apex toward the hilum

(10) Syphilis of the lung, which may be associated with unilateral pleuropulmonary fibrosis

(11) Interstitial pneumonitis

(12) Virus pneumonia (atypical pneumonia) of unknown origin

(13) Influenzal pneumonia

(14) Manifestations of pulmonary infection caused by bacteria, rickettsial micro organisms, fungi, protozoa or parasites Tuberculosis is of particular importance in this group

(15) Pulmonary sarcoidosis

(16) Collagen diseases of the lung (Lupus erythematosus and scleroderma)

(17) Xanthomatosis with pulmonary changes

(18) Benign tumors of the lung, pleura and pericardium

(19) Malignant tumors of the lung, pleura and pericardium

(20) Lymphomatoid diseases with lung changes.

(21) Pulmonary adenomatosis

(22) Arteriovenous fistula of the lung

(23) Congenital hypogenesis of the lung

(24) Thickening of the pleura due to inflammatory changes

The characteristics of the various conditions mentioned are discussed in detail in the respective chapters

Treatment

Prevention of radiation pleuropulmonitis is of utmost importance The responsibility in this respect should be shared by the attending physician, surgeon and radiologist Only through their joint evaluation and decision is it possible to promote the welfare of the patient Due consideration of individual clinical findings makes the difference between personalized and mechanized medical care

It has been emphasized by a number of radiologists that one can avoid radiation damage to the lung in cases of breast cancer, provided the preoperative x ray treatment is given tangentially, with precise technique, focusing the beam of radiation through the breast only from mesial and lateral directions

Following the demonstration of Boys and Harris that pathologic pulmonary changes due to irradiation in heparinized experimental animals

are less than in the controls, Macht and Perlberg resorted to the clinical use of anticoagulants for the prevention of tissue changes in the lung resulting from x ray irradiation They used dicumarol for this purpose They report that the administration of this drug prevents radiation changes in the lung when the customary therapeutic doses of x ray are given Dicumarol is administered at the same time as x ray therapy They point out that it is very difficult to maintain the patient on a constant prothrombin level Precise observations and prompt adjustment of the dosage given are required for accurately and safely lengthening the prothrombin time The patient should be kept at the hospital during the entire course of treatment

Cosgriff and Kligerman employed corticotropin (ACTH) and cortisone in the management of this condition They observed partial reversal of acute symptoms with this medication Two months after the discontinuance of the drugs however development of atelectasis and fibrosis was observed

Considerable attention to details is necessary in the management of patients with extensive radiation fibrosis of the lung and pleura One should be alert to the possibility of superimposed infection of the lower respiratory tract and administer adequate doses of antibiotics (penicillin streptomycin aureomycin chloramphenicol) and other drugs for their control as promptly as possible Pain and protracted unproductive cough should be checked Unproductive cough is harmful on account of its damaging effect upon the elastic fibers of the lung and on the alveoli In addition to prescribing potent cough sedatives, it is well to keep in mind that in some instances cough can be satisfactorily relieved by removing sticky tenacious secretions Inhalation of 5 per cent carbon dioxide with 95 per cent oxygen through a face mask for 15 minutes several times a day is an excellent means for liquifying a thick, adherent stagnating exudate in the bronchial tubes In this manner, expectoration is facilitated, excessive cough alleviated and the need for the continued administration of narcotics is eliminated

Directions concerning measures for the treatment of cor pulmonale and its complications are presented in the chapter on Pulmonary Fibrosis

Leach and his associates recommended reducing diet when the patient is overweight so as to alleviate dyspnea Also, they introduced the use of special abdominal support for the treatment of dyspnea of these patients They noted highly satisfactory results from its use Christie and Alexander and Kountz, in 1943, advocated the use of a suitable abdominal binder

for the symptomatic treatment of emphysema. The rationale of this recommendation is based on the observations that

(1) In emphysema, the diaphragm occupies an abnormally low position which obviates its normal respiratory excursions,

(2) An abdominal binder not only raises the diaphragm toward its expiratory position, but also supports this muscle and thereby prevents its paradoxical movements,

(3) When the diaphragm is lifted from its abnormally low position to a high level in persons with emphysema, the intrapleural pressure becomes more negative and thus, lung function is improved Gordon (1934, 1935) constructed an abdominal support for the treatment of various pulmonary conditions With its use, he observed elevation of the diaphragm from 1 5 to 3 5 cm

Benefits derived from the use of abdominal supports in radiation pleu ropulmonitis are attributable to a consequent increase in the functional ompetency of the diaphragm When the fibrotic changes are localized ..t the upper and middle one thirds of the lung the respiratory capacity of the lower one third of the affected lung is ameliorated with a sim taneously augmented function of the opposite lung Of course, whe hemidiaphragm is already fixed by adhesions in a high position or virtually the entire extent of one lung is involved, relief from d can be expected from wearing an abdominal support through on the nonfibrotic, emphysematous lung on the opposite side Le colleagues recorded an increase in the vital capacity of the measure in some of these patients which varied from 200 to they noted a decrease in the minute ventilation by 5 to 10 may be sufficient to relieve dyspnea Banyai (1938) demo much greater elevation of the diaphragm could be obtained pneumoperitoneum than with an abdominal support His studies showed that satisfactorily established and mainta peritoneum may raise the diaphragm by more than 7 cm other terms, artificial pneumoperitoneum is capable of diaphragm so that the apico-basal diameter of the lung by more than 32 per cent of its original length Natura from dyspnea can be anticipated in these patients from peritoneum than from an abdominal belt Therapeu neum is a simple and safe procedure which can be physician of average manual dexterity With asept local anesthesia, air is injected into the peritoneal cav

fingers' breadth below and to the left of the umbilicus From 500 to 600 cc of air is given with the first treatment, and the same amount four days later From then on, weekly injections are administered with 500 to 700 cc of air An ordinary 19 gauge, 2½ inch needle and a standard pneumothorax apparatus are used Pneumoperitoneum treatment is well tolerated by the patients and can be maintained for years Technical and other pertinent details of this method are described in Banyai's monograph on the subject

Radium

Radium deserves special mention as a possible source of radiation pleuropulmonitis In Engelstad s patient, treatment with teleradium (radium skin distance 5 6 cm) was followed by widespread pulmonary infiltration Some months later, the lung changes, as seen on the roentgenogram, diminished, but subsequently, pronounced fibrosis developed in the treated lung, with contraction of the corresponding hemithorax The aforementioned table of Leach and his associates gives the incidence of roentgenologically demonstrable lung changes in patients treated with radium

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CHAPTER V

PULMONARY MYCOSES

By ALVIS E GREER M D

ACTINOMYCOSIS

PRELIMINARY CONSIDERATIONS DEALING WITH SYSTEMIC PATHOGENIC FUNGI

Foreword

A DISCUSSION of pathogenic pulmonary mycoses would not be complete without considering their fundamental characteristics In the following preliminary remarks considerations dealing with the methods of collection and macroscopic study of the specimen, cultural methods, staining techniques, animal inoculation, determination of morphology, nomenclature, practical classification and microscopic appearance of fungi will be discussed

The Isolation and Identification of Pathogenic Fungi

Collection of the Specimen

It must be remembered in this connection that many of the fungi of pulmonary mycoses are systemic as well and invade the other internal organs of the body, as for instance the liver, spleen, kidneys, the cutaneous and subcutaneous tissues and mucous membranes Therefore, specimens may be obtained from a wide variety of localities and aid in the diagnostic problem under consideration Examination of pus from discharging sinuses aspirated fluid from subcutaneous and open abscesses, scrapings from ulcerative skin lesions, sputum, bronchial washing, blood, sternal bone marrow, spinal fluid, biopsied lymph nodes and other tissues may be done if the individual diagnostic problem suggests one or more of these procedures This is for the clinician to decide It must be stressed that diagnosis is not affirmative unless the causative fungus is isolated One of the main essentials is for the amount of the specimen to be adequate with which to work The best time to collect sputum is early in the morning just after the

patient awakes. The patient is instructed to expectorate in a sterilized petri dish after he has carefully brushed his teeth and rinsed and gargled his mouth and throat Care should be taken that saliva is not expectorated and that the sputum is raised from the lungs The sputum so collected should be examined with a hand lens and small flecks selected for microscopic study and culture

Macroscopic Study of Specimen

One or several of these flecks is placed on a clean glass slide One or two drops of 10 per cent sodium hydroxide is added and mixed carefully In some instances fungi may be found in the fresh specimen, but if not found the sputum must be concentrated, and by the latter method the causative fungus may be found It is always desirable that smears be obtained Gram s stain and Wright's stain are satisfactory Iron-alum hematoxylin and the Hotchkiss-McManus periodic acid stains for biopsied materials give good results

Cultural Methods

A common misconception is that Sabouraud's medium is the medium of choice on which to grow all fungi This is in error, as for instance the Actinomyces bovis will not grow on Sabouraud's medium Different fungi have diverse nutritional requirements for growth, and therefore various types of media must be used in identifying them The following media have been recommended for the purposes indicated, cornmeal agar for differentiation of yeasts and Cryptococci rom species of Candida and for the recognition of Candida albicans, lextrose nutrient agar and blood agar, to which 25 units per cc each f penicillin and streptomycin has been added, for Histoplasma capsulam, Coccidioides immitis and the Blastomyces, dextrose nutrient agar d blood agar, without penicillin and streptomycin for Nocardia, oglycollate broth for both Actinomyces bovis and Nocardia asteroides

Many of the pathogenic fungi grow very slowly Cultures of fungi should be incubated both at 30 degrees C and 37 degrees C Blastomyces dermatitidis and B brasiliensis and Histoplasma capsulatum grow in two phases– filamentous at 30 degrees C and yeastlike at 37 degrees C It is well to keep all cultures for three or four weeks before being discarded Candida albicans, Aspergillus fumigatus and Geotrichum grow on culture within 48 hours, Cryptococcus neoformans

within 72 hours, Actinomyces, Coccidioides, Sporotrichum, Histoplasma and Blastomyces within 10 days, although these latter fungi may show growth on the medium in 2 to 4 days

We have found besides the above mentioned media, the following culture materials of considerable usefulness meat infusion broth with or without the addition of glucose and blood, dextrose yeast extract medium, dextrose blood agar, brain heart infusion agar and nutrient agar The formulae for these media may be found in any good laboratory manual and it will not be necessary to give them here In addition to using cultures in standard glass tubes and petri dishes, we have found glass slide cultures of considerable help Slide cultures may be made with either liquid or solid media It is imperative that the cover glasses and slides be quite clean A few cubic centimeters of melted Sabouraud s agar are poured on a clean 2 x 3 inch glass slide, allowed to solidify and the surface inoculated with a loopful of sputum or exudate This preparation is covered with a clean No 1 cover glass which is then rimmed with vaseline A small aperture at one side of the slide is left open for the ingress of air To prevent excessive dehydration the prepared slide culture is placed on a layer of moist cotton in the petri dish Incubation may be at either 30 degrees C or 37 degrees C, or both, if two slides are prepared This is an interesting and important procedure because one may watch the development and multiplication of the fungus at regular intervals

Staining of Fungi

We have found Amann's mounting fluid, lactophenol cotton blue, preferable It serves as a combined fixing agent, stain, and mounting fluid The spores and the mycelium will be stained blue A disadvantage is that the preparation is not permanent Semi permanent and permanent preparations may be made by growing the molds directly on slides with cover glasses Sealing the edges of the cover slips with nail polish, asphaltum or other varnishes may convert the temporary slides into semi permanent ones Flooding the cover slips with balsam will have a like effect Henrici has advised, if permanent preparations are desired, glycerin jelly be used instead of Amann's fluid Other stains Gram, Giemsa, Wright, India ink, to mention a few, are of course useful

Stained smears are relatively of less help than cultures in examining clinical materials Henrici states frankly that stained smears are not

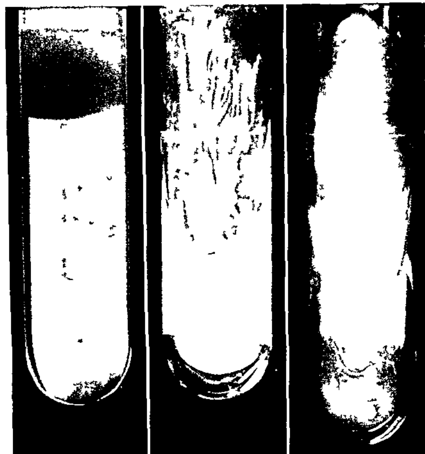


Fig 1 Actinomyces bovis A deep culture on Emmons's medium reveals whitish to yellowish cuneiform colonies

Fig 2 Nocardia asteroides Culture on Emmons's medium Shows confluent irregularly shaped verrucose colonies of a pale yellowish orange color and mealy consistency

Fig 3 Blastomyces dermatitidis Culture on Emmons's medium. Shows a wooly type of growth yellowish white in color

of much use in detecting pathogenic fungi in exudates There are exceptions to this rule, sporotrichosis may be best demonstrated in smears of pus other exceptions are infections with Cryptococcus Candida and Histoplasma The following stains are valuable in clinical materials for certain specified conditions Gram stain for suspected moniliasis and actinomycosis acid fast stain in suspected nocardiosis methylene blue Gram's method or India ink preparations in suspected

cryptococcosis, Giemsa, Wright's or Wilson's stain in histoplasmosis.

The staining of biopsied tissue may be made with the Gram Weigert Unna's modification of the Unna Pappenheim stain or preferably with the Hotchkiss McManus periodic acid stain

Animal Inoculation

Animal inoculation may be advisable in some instances when cultures fail to demonstrate the fungus Most laboratory animals are

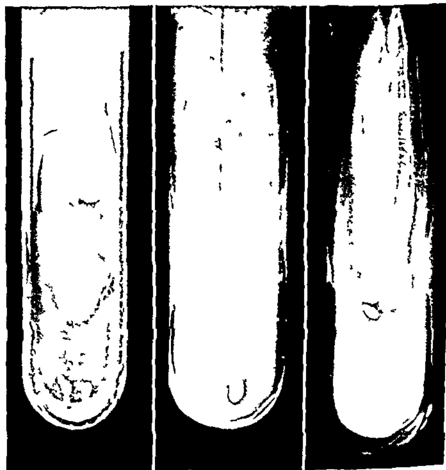


Fig 4 Blastomyces brasiliensis Culture on Emmon's medium Shows white and cottony colonies with an irregular heaped up appearance

Fig 5 Coccidioides immitis Culture on Emmon's medium Shows loose cottony creamy white colonies forming concentric circles

Fig 6 Candida albicans Culture on Emmon's medium Shows thick membranous colonies of a creamy white color and velvety appearance



Fig 7 Sporotrichum schenckii Culture on Emmons's medium Surface is moist and shiny light tan in color and reveals several dark areas of coffee brown color

Fig 8 Histoplasma capsulatum Culture on Emmons's medium. Shows hyphal type of growth appearing as a white cottony mold

Fig 9 Cryptococcus neoformans Culture on Emmons's medium. Shows whitish yellow colonies which are heaped up pasty shiny and thick

somewhat resistant to fungus infections It has been found by Spring that mice are the most susceptible guinea pigs more resistant and rabbits practically immune Benham has stated that dogs and monkeys are most susceptible The following table by Charlotte C Campbell summarizes the known facts regarding animal inoculation with pathogenic fungi

TABLE I
ANIMAL INOCULATION WITH PATHOGENIC FUNGI

Organ sm	An mal of *Choice*	Inoculat on *Route*	Exposure *Interval*	Gross Pathology *(lesions)*	M croscopic Find ngs
N Astero des*	Gu nea P g	Intrape itoneal	8 10 days	Mesentery Pe itoneum	Ac d fast branch ng filaments
C Neoformans*	Mouse	Intraj e itoneal	1 4 weeks	Pe itoneum b a n spleen gelat n n us ma es in mesentery	Budd ng encapsula ed yeasts
C Alb cans	Rabb t	Intraveno s	4-6 days	Ab cesses through pe toneum and k dney	Th n walled budd ng yea ts with o w thout pseudomycel a
B D					
B B					
H Capsulatum*	Mouse	Intraper toneal	2 3 weeks	Mesentery d aph ragm v sceral o gans	Small oval budd ng cells
S Schenck *	Male Rats	Intratest cular	1-4 weeks	Per ton tis o ch t s	Clear shaped budd ng cells
C Imm tis	Male Gu nea P g	Intratest cular	10 15 days	orch t s	Do ble walled sphe ical bod es conta n ng en dospores

fi

F

death has not meanwhile ensued

It has been suggested that in inoculating guinea pigs with Actino myces, inoculations should be begun with small sublethal doses and increasingly larger doses be repeated at regular intervals for several weeks This method is more likely to be successful than one primary injection, which oftentimes fails to produce pathology I am of the opinion this method might be of value in the study of other pathogenic fungi because after a time the tissues of the inoculated animal will become sensitized and a large dose of the fungus would then cause a more widespread systemic involvement than by the one injection

Determination of Morphology

The identification of fungi is dependent largely upon distinctive morphological characteristics and their modes of reproduction It is somewhat confusing to the beginner that the gross morphology and the microscopic characteristics of a given fungus may vary with the composition of the medium, the age of the culture and in some instances the temperature sustained during incubation In regard to the temper ature of incubation it is well to remember that the optimum temper ature for growth for most of the pathogenic fungi is not at body tem

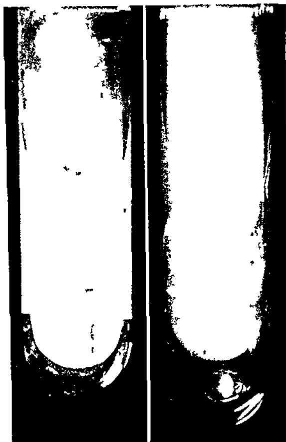


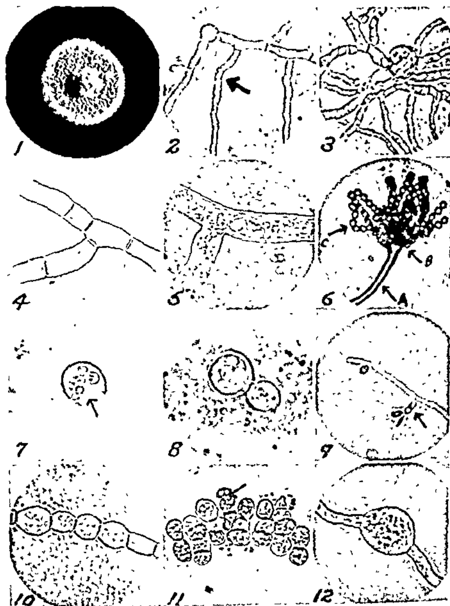
Fig 10 Aspergillus fumigatus Culture on Emmons's medium Shows a mottled wooly appearance and a dark green color

Fig 11 Geotrichum candidum Culture on Emmons's medium Shows a firmly adherent felt like mass pure white in color

perature but at a lower level of approximately 30 degrees C It is probably best, however to place parts of a specimen to be analyzed in two different culture plates and incubate them at diverse temperatures, namely, at 30 degrees C and 37 degrees C, respectively We have stated heretofore that certain fungi as Blastomyces dermatitidis, Blastomyces brasiliensis and Histoplasma capsulatum develop as filamentous at 30 degrees C and yeastlike at 37 degrees C These differences of growth have definite diagnostic importance

It is advisable for the clinician to be conversant with the various

component parts of the fungus because diagnostic differentiation of the pathogenic fungi is facilitated thereby. This objective may be obtained best by including at this point some illustrations by Joseph M. Kurung of the component parts of the fungus together with their descriptive terms.



Practical Classification of Pathogenic Fungi Affecting the Lung

A Bacteria like
  1 Actinomyces bovis
  2 Nocardia asteroides
B Yeastlike
  1 Cryptococcus neoformans
  2 Candida albicans
  3 Geotrichum candidum
C Yeast Mold
  1 Blastomyces dermatitidis
  2 Blastomyces brasiliensis
  3 Histoplasma capsulatum
  4 Sporotrichum schenckii
D Molds
  1 Coccidioides immitis
  2 Aspergillus fumigatus

All of the pathogenic fungi except Actinomyces and Nocardia species, belong to the class Fungi Imperfecti in which no sexual cycle of reproduction has been demonstrated

Microscopic Appearance of Fungi

It has been stated heretofore that the true relationships of the various fungi are indicated by minute cell characteristics and their modes of reproduction The reproductive mycelium and its spores are different in diverse types of fungi and serve to identify and classify them I am appending microphotographic prints of the pathogenic fungi which should show graphically the differing characteristics which identify them



Fig 12 The isolation and identification of pathogenic fungi from sputum (Courtesy Joseph M Kurung *Am Rev Tuberc* 55 387 411 (May) 1947)

Fig 12 (1) Thallus—or colony (2) Hypha—one of the filaments (3) Mycelia—a collection of hyphae (4) Mycelia—septate having subdivisions of hyphae (5) Mycelia—non septate hyphae without subdivisions (6) Sporehead (Aspergillus) a) Conidiophore mycelial stalk bearing conidia, (b) Vesicle the swollen portion of the conidiophore (c) Conidia the spores (7) Endospores—spores formed within the parent cell (8) Blastospores or budding forms—spores developed by budding from the side of the parent cell (9) Sporophore—that part of the hypha which bears the spores (10) Arthrospores—segmentation of the hypha into chains of cells (11) Ascospores—spores formed within a sac called an ascus The spores are limited in number to two four or eight depending on the species producing them (12 Chlamydospores a swollen portion of the hypha. A resting spore which may be terminal lateral or develop along the hypha.

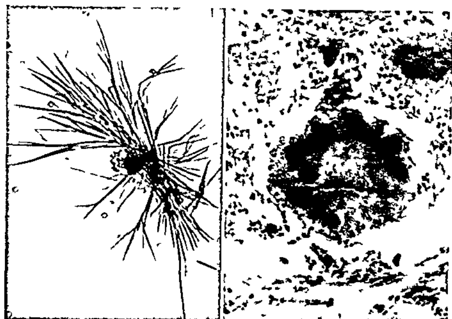


Fig 13 Actinomyces bovis (430x) Lactophenol cotton blue stain Shows very slender branched mycelium less than 1 micron in diameter showing suggestion of septation in some hyphae and coiled chains of conidia to the left of the central area.

Fig 14 Actinomycotic granule ('sulfur granule) 440x. Shows the characteristic *lobulated structure consisting of a central core of tangled branching filaments* and extending peripherally hyphae having a radial appearance and ending in club-shaped structures The central portion stains a deep blue color while the outer edge, or clubbed ends stain pink

It has been my objective in presenting this section, preliminary to the discussion of the various pathogenic fungi affecting the lungs in the ensuing section that the busy clinician will benefit by this brief *review of the procedures necessary to identify and classify such fungi*

Actinomycosis is a chronic granulomatous disease due to the anaerobic Actinomyces bovis, characterized by the production of multiple abscesses and sinuses in the head and neck, abdominal and thoracic organs, as well as other organs of the body to a lesser degree A diagnostic feature is the finding of *sulfur* granules in the drainage from the fistulae

In discussing pulmonary actinomycosis it is to be stressed that 90 per cent of the cases are due to the anaerobic Actinomyces bovis, in which *sulfur* granules are usually present, but in 10 per cent, the acid fast, aerobic Nocardia asteroides is found Henrici has suggested the latter condition might better be called nocardiosis These two forms of actinomycosis may be differentiated only by the isolation and differentia-



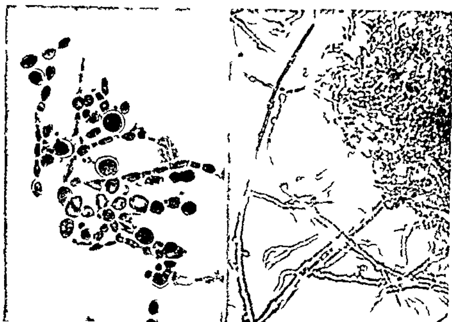
Fig 15 Nocardia asteroides (1100x) Lactophenol cotton blue stain Shows branching slender mycelia 0 2 microns in diameter with nearly spherical spores in chains

Fig 16 Blastomyces dermatitidis (430x Young (6 day) culture on blood agar at 37 degrees C Shows transitional forms from the yeastlike to the mycelial form. The spherical pyriform or oval conidia are lying free as well as budding directly from the hyphae

tion of the causative fungus since the clinical aspects of the two types are alike except that the outlook for patients with Nocardia asteroides infection is exceedingly grave in contrast to the outcome of Actinomyces bovis infections

Actinomycosis has been observed in almost all domesticated animals, with a predilection for the herbivorous ones especially cattle in which the infection occurs usually in or about the mouth and the alveolar bones It is more prevalent in the midwestern part of the United States The portal of entry is the mouth of the patient, notably about the teeth or the tonsils It has been affirmed that the fungus may occur in the oral cavity *as a saprophyte In cattle the disease is most likely transmitted* through contaminated fodder The disease in man may likewise be attributed to contact with the foodstuffs of infected animals

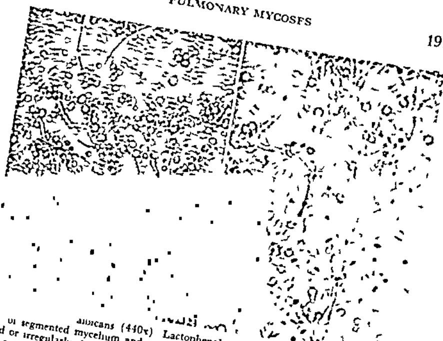
The characteristic lesions are suppurating sinuses with considerable new connective tissue and resulting scar formation There may be variation in the stages of healing of the abscesses and their connecting fistulae,



F g 17 Blastom)ces bras l ens s (430x) Lactophenol cotton blue sta n Shows large th ck walled mult ple budd ng yeastl ke cells 5 to 50 m crons n d ameter

F g 18 Cocc d o des mm t s (440x) Lactophenol cotton blue sta n Shows a tan gled mass of branch ng septate m)cel um g ng r se to racquet mycel um and chlamydospores and arthrospores

in that the process may be active in one place and healed in a contiguous area Multiple discharging fistulae are usuall) present and in the sanguino purulent pus the *sulfur* granules or the branch ng fungus filaments ma) be found The disease spreads by continuit) and lymphatic and hematogenous dissemination is rare S nce the histologic diagnosis may be considered positive only by find ng the *sulfur* granules its known characteristics are of great importance It has heretofore been stated that f nd ng of separate mycel al segments is suggestive The *sulfur* granules are composed of intertwined branch like m)cel a with characteristically radially constructed club like enlargements—the so called ray fungus *These granules ma) be of microscopic size or large enough to be visible* to the naked e)e Polymorphonuclear cells usuall) surround the granules although giant cells ma) be present Material obtained by biopsy best from within small abscesses may or may not contain *sulfur* granules and present only a suppurative infection or cells of a chron c inflammatory process There are four types of actinom)cosis affecting the lungs namel) the bronchitic the pneumonic the pleuropneumonic types and lastl)



F... albicans (440x) Lactophenol cotton blue stain Shows a tangled ... of segmented mycelium and scattered throughout many budding yeastlike cells ovoid or irregularly shaped

Fig 20 Sporotrichum schenckii (550x) Lactophenol cotton blue stain Shows a tangled mass of branching septate mycelium and a great number of pear shaped conidia mainly attached to the hyphae, but showing many detached conidia

metastatic nodules The first three types are different stages of the same process, beginning with pus and fungi in the bronchi, which spread t[o] the surrounding alveoli, producing areas of bronchopneumonia Th[e] alveoli are filled with pus, and later connective tissue formation begin[s] to take place in the alveoli earliest affected, causing hard fibrous nodules which alternate with softened areas and abscesses The picture varies greatly, for there may be no attempt at healing, and the alveolar walls may be lost, and large abscesses containing pus and fungi may be found We may find bronchi filled with pus, nodules of connective tissue, and abscesses of varying size As the abscesses enlarge and burrow to the pleural cavity, the pleuropneumonic type is formed From this point onward the pus frequently invades the chest wall The metastatic nodules are supposed to be of hematogenous origin, but it is difficult to understand, if this supposition is true, why other organs of the body are not likewise invaded

Actinomycosis of the thoracic organs constitutes 15 per cent of the

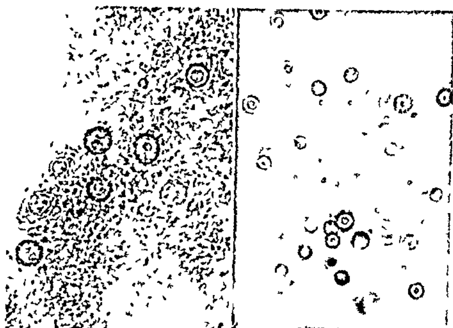


Fig 21 *Histoplasma capsulatum* (430x) Lactophenol cotton blue Shows the characteristic large thick walled round or pyriform tuberculated chlamydospores spherical in shape varying in diameter from 7 to 20 microns showing the outer wall adorned with wart like occasionally spiny excrescences

Fig 22 Cryptococcus neoformans (900x) Lactophenol cotton blue stain Shows budding cells varying greatly in size surrounded by clear halos representing the exceedingly thick capsular material Buds may be seen arising as small projections from the parent cell showing the narrow connection between the mother and daughter cell

cases, the cervicofacial accounting for 50 per cent, the abdominal 20 to 30 per cent, the other organs and skin 15 per cent We are concerned in this discussion with the thoracic organs solely It is to be remembered the clinical symptoms and course will vary greatly depending on the stages of the disease The primary infection, resulting, perhaps, from aspiration of infected material from the mouth into the bronchi, resembles any acute or subacute pulmonary disease with moderately productive cough and irregular fever When the alveoli become involved, and the pneumonic stage with small abscesses in the lungs develops, the symptoms become augmented—cough with mucopurulent sputum, at times fetid or bloody, dyspnoea, chills, spiking fever night sweats loss of weight, anemia, and weakness If the pus is abundant, *sulfur* granules or tangled masses of mycelia may be found in the sputum As the infection spreads to the pleural membranes, extremely severe pain will be experienced by the patient A pleural effusion may develop, but more

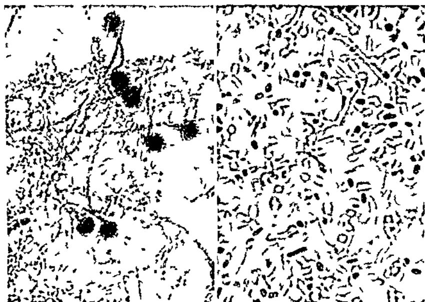


Fig 23 Aspergillus fumigatus (430x) Lactophenol cotton blue stain Shows the branching septate hyphae enlarging toward the top to the conidiophores which hold flask-shaped vesicles crowded with sterigmata which give rise to parallel chains of conidia

Fig 24 Geotrichum candidum (430x) Lactophenol cotton blue stain Shows branched septate mycelia and numerous large square ended arthrospores

commonly, the infection invades the chest wall directly, producing subcutaneous abscesses or draining sinuses in the subcutaneous tissues The further course of the disease exhibits a tendency toward chronicity but withal a gradual downhill course, and extensive deterioration of the individual s resistance to the infection and impairment of the pulmonary function The patient will become emaciated, extremely anemic, dyspnoeic, prostrated with fever of an irregular spiking type, septic, exhausted, and death will ensue

The physical signs will vary greatly depending upon the stage in which the patient is first seen In the beginning the diagnosis will be impossible to make from the symptoms and physical signs alone This is true of both the bronchitic and the pneumonic phases Especially in the latter stage the clinical course resembles closely that of tuberculosis The diagnosis in such a case would of necessity depend upon finding the *sulfur* granules or fungus in the sputum but usually they are not found in the sputum until the abscess has progressed to its terminal phase An important

differential point is that the primary areas of pulmonary localization in actinomycosis are in the lung bases and are bilateral, whereas in tuberculosis the original pathology is usually above the third rib and is unilateral It is later that massive areas of dullness develop, the chest wall is retracted and limited, and the heart displaced By this time the presence of subcutaneous abscesses and draining sinuses will suggest the diagnosis of actinomycosis The finding of the fungus granules in the walls of these abscesses or sinuses clinches the diagnosis of pulmonary actinomycosis

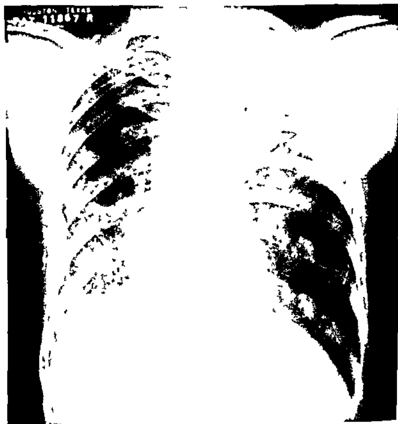


Fig 26 Pulmonary Actinomycosis In the upper third of the left lung a large area of smooth density extending to the pleura, in which are seen irregular areas of rarefaction in the central portion At the base of the right lung an irregularly formed density involving the costophrenic sulcus and pleura, a pleurocutaneous fistula was present at this area

The *roentgenogram* will present a puzzling picture It may show one or several large consolidations, small nodules, or/and pleural fluid The

areas of consolidation present irregularly formed smooth, large areas without cavitation, or at the most small irregular areas of rarefaction Usually the lesions are bilaterally situated in the basal areas although any part of the lung may be involved There may be evidences of pleural fluid or extensive pleural adhesions and destructive proliferative processes observed in the ribs

The disease is to be differentiated from tuberculosis bronchiectasis lung abscess, or tumors of the lung Christianson and Warwick have a table differentiating tuberculosis and actinomycosis which is simple and helpful

Actinomycosis	Tuberculosis
Lower lobe of lung first affected	Apex first affected
Lymph nodes never involved	Lymph nodes usually involved
Pain a common symptom	Pain a rare symptom
Cavity formation rare	Cavity formation frequent
Fungi found in sputum	Tubercle bacilli found in sputum
Spreads by continuity	Often metastasizes through blood
Sinuses often present in chest wall	No involvement of chest wall
Abscess formation frequent	No abscess formation
Often spreads through diaphragm	Very rarely spreads through diaphragm

Actinomycosis is so varied in its clinical manifestations that many other conditions must be considered in the differential diagnosis The diseases which may at one time or another cause confusion in the diagnosis are actinobacillosis staphylococcic actinophytosis (botryomycosis) syphilis, tularemia, osteomyelitis sporotrichosis blastomycosis coccidioidomycosis and cryptococcosis

The prognosis heretofore has been considered very bad until the advent of the sulfonamides and penicillin These drugs have given us renewed hope, especially for the earlier cases

In the treatment of actinomycosis even with the promise of the sulfonamides and penicillin adequate surgical drainage is necessary and the use of iodides advisable Whatever other adjuncts are used the iodides are always included in our therapeutic regimen The saturated solution of potassium iodide is given by mouth beginning with 5 drops well diluted in water, three times a day after meal gradually increasing by 1 drop a day until 25 drops of the drug are given three times a day, the

connective tissue, in conjunction with surrounding infiltration with lymphocytic cells, polymorphonuclear leucocytes, and plasma cells, occasionally endothelioid cells and *giant cells are found*. The rete may extend deeply into the tissues, and long, thin projections extend into the inflammatory area. A characteristic feature is the hyperplasia of the epithelium and the numerous tiny abscesses found therein. The fungi may be found outside the cells and within the giant cells in the miliary abscesses. The lung is the most frequently affected organ in systemic blastomycosis. There may be found in the lung tissue, small or large yellowish fairly discrete nodules, resembling the tubercle, or areas which are produced by the confluence of many small or large nodulations. The nodules soften and abscesses form. Cavities although infrequent, may occur. A pleurisy, or fibrosis of the pleural membrane, and occasionally an *osteomyelitis of the ribs may ensue*. The pericardium may become involved. Dissemination of the infection into the subcutaneous tissue or bones and throughout the body may result. In approximately one third *of the cases the central nervous system becomes affected* by either a basilar meningitis or blastomycotic nodules throughout the brain tissue.

The mortality of cutaneous blastomycosis is only about 10 per cent whereas, in systemic blastomycosis practically all patients die of the disease.

There are two clinical types of blastomycosis recognized, the cutaneous and the systemic. The onset of the pulmonary form is insidious and dissemination may occur before the diagnosis is made. The initial symptoms are those of an ordinary acute respiratory disease with a nonproductive cough, low grade fever, chest pains, and moderate dyspnoea. Within several weeks or months the symptoms become augmented, the cough becomes productive, with purulent, at times, bloody sputum, great loss of weight and strength, considerable fever, increased dyspnoea, and night sweats. The mediastinum usually becomes involved, with invasion of the heart and the pericardium. The disease, then, becomes disseminated, and symptoms of invasion of other organs become evident. In most of the cases skin lesions eventually develop.

The pulmonary physical findings are similar to those of lung abscess or massive pulmonary tuberculosis, with dullness and depressed breath sounds. Rales are not constantly found, however. There may be discharging sinuses or abscesses present, either over the chest or elsewhere on the body.



Fig 27 North American Blastomycosis

The most characteristic roentgenologic finding is enlargement of the mediastinal shadow which projects in irregular dense masses into the pulmonary parenchyma As a rule these shadows are unilateral in the beginning but often the infection spreads to the opposite side When cavitation is seen the cavities are small hazy and irregular When the infection is the result of hematogenous dissemination relatively small nodules not unlike miliary tuberculosis are seen throughout the lung fields

Pulmonary blastomycosis should be differentiated from coccidioido-

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cosis when the iodide treatment is supplemented by desensitization with the vaccine, careful roentgen ray use, and surgery, if indicated

The iodides may be given in one or two ways, the slow, and the rapid method The slow method consists in giving 3 drops of saturated solution of potassium iodide three times a day, increasing one drop daily, until the patient receives 20 drops three times a day The dose is then reduced gradually to the initial dosage, and again, increased to 20 drops three times a day This is the preferable method The more rapid method consists of beginning with 5 drops three times a day, and increasing 1 drop each dose, or 3 drops a day It may be increased to 100 drops three times a day Sodium iodide intravenously in a daily dose of 1 gram may be given Ethyl iodide inhalations, using an inhaler made by the Warren Collins Instrument Company of Boston, may be combined with the oral administration of iodides

Fishman has reported the cure of a case of disseminated blastomycosis by the use of ether Elson in 1945 reported that certain of the aromatic diamidines exert a fungistatic effect on Blastomyces dermatitidis in vitro Schoenbach *et al* have reported favorable results with the two diamidines stilbamidine and propamidine, in the treatment of systemic North American blastomycosis

The use of x ray therapy is at times indicated in pulmonary blastomycosis, but must be given in reduced dosage and cautiously used

The indication for surgery is the drainage of accumulations of pus

SOUTH AMERICAN BLASTOMYCOSIS (PARACOCCIDIOIDAL GRANULOMA)

South American blastomycosis is a highly fatal, chronic granulomatous disease of the skin, mucous membranes of the mouth, nose, and gastrointestinal tract, lymph nodes, and the internal organs, notably the spleen, liver, and seldom the lungs, caused by the fungus Blastomyces brasiliensis The disease has a predilection for lymphatic tissues Many of the earliest cases were confused with coccidioidomycosis, later investigators show the fungus produces by budding, and consequently the disease was classified among the blastomycoses

Although the origin of the disease is unknown, it is probably contracted exogenously, and is most commonly found in young male outdoor laborers Strictly a South American disease, almost exclusively limited to Brazil, only a few cases have been reported in Argentina, Paraguay, Peru, and Venezuela

mycosis, South American blastomycosis, sporotrichosis, cryptococcosis, moniliasis, and actinomycosis, tuberculosis, syphilis, lung abscess, neoplasm, sarcoidosis, and silicosis

The diagnosis may be established by finding the budding yeast like fungi in the sputum or in the pus from the minute abscesses of the skin Ordinary routine laboratory tests are of no value, *there is usually* a secondary anemia and leucocytosis It is my opinion, because there are definite cultural relationships between Blastomyces dermatitidis and Histoplasma capsulatum, and that immunological cross reactions as demonstrated by skin testing with blastomycin and histoplasmin that the skin test is not of itself diagnostic It may be that this cross reactivity with histoplasmin is directly related to the strain of the histoplasma antigen and the size of the test dose The skin test is of value, however, in determining the therapeutic regimen The blastomycin skin test is performed by injecting 0 1 ml of a 1 1000 dilution of a broth filtrate intradermally The interpretation is identical with that of tuberculin test The complement fixation test alone is not a reliable diagnostic measure in blastomycosis because some individuals do not produce antibodies although in most cases the test is positive A considerable number of articles have appeared in the literature which indicate the possible course and final outcome depend in large measure on the allergic or immunologic response of the patient to the infection It has been proved that a high antibody titer and a negative skin test indicate an unfavorable prognosis, whereas, the reverse findings, a negative complement fixation and a positive skin test denote a more favorable clinical course

The prognosis in blastomycotic infections is very bad Most patients (90 per cent) succumb within five years after the initial onset of the disease

The administration of iodides, since it was first advocated by Gilchrist, has been found to be the sheet anchor of therapy Its use, however, is not without danger, when given to patients who have become highly sensitized to their infection Patients who have reacted strongly to the intracutaneous blastomycotic vaccine, indicating marked hypersensitivity, should be desensitized before iodides are given For otherwise, such patients may not improve, but grow rapidly worse on iodide therapy

Best results will be obtained in the treatment of systemic *blastomy*

cosis when the iodide treatment is supplemented by desensitization with the vaccine careful roentgen ray use, and surgery, if indicated

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Fishman has reported the cure of a case of disseminated blastomycosis by the use of ether Elson in 1945 reported that certain of the aromatic diamidines exert a fungistatic effect on Blastomyces dermatitidis in vitro Schoenbach *et al* have reported favorable results with the two diamidines stilbamidine and propamidine, in the treatment of systemic North American blastomycosis

The use of x ray therapy is at times indicated in pulmonary blastomycosis, but must be given in reduced dosage and cautiously used

The indication for surgery is the drainage of accumulations of pus

SOUTH AMERICAN BLASTOMYCOSIS (PARACOCCIDIOIDAL GRANULOMA)

South American blastomycosis is a highly fatal, chronic granulomatous disease of the skin, mucous membranes of the mouth, nose, and gastrointestinal tract, lymph nodes, and the internal organs, notably the spleen liver, and seldom the lungs, caused by the fungus Blastomyces brasiliensis The disease has a predilection for lymphatic tissues Many of the earliest cases were confused with coccidioidomycosis, later investigators show the fungus produces by budding, and consequently the disease was classified among the blastomycoses

Although the origin of the disease is unknown, it is probably contracted exogenously, and is most commonly found in young male outdoor laborers Strictly a South American disease, almost exclusively limited to Brazil, only a few cases have been reported in Argentina, Paraguay, Peru, and Venezuela

The infection has been classified into four clinical types (1) a cutaneous form affecting the skin and mucous membrane of the oral and nasal passages, (2) the lymphatic type, first observed as a nodular lesion of the neck or supraclavicular or axillary lymph nodes, (3) a visceral type, affecting the intestines, liver, spleen, pancreas, and other abdominal organs, and the lungs, and (4) a mixed type, which comprises a combination of the cutaneous, lymphatic and visceral forms

The usual lesion is in the mucous membranes, wherein a small papule develops and rapidly ulcerates These lesions spread quickly, neighboring lymph nodes enlarge and coalesce, soften, break down, and sinuses develop into the skin *Dissemination occurs by way of the bloodstream,* and a widespread invasion of the spleen, liver, and other internal organs results The lungs are invaded hematogenously from the primarily affected areas and there is no proof that the infection occurs primarily in them The pulmonary lesions are seen as diffuse and nodular infiltrations The cutaneous and the buccal lesions are very characteristic and the rapidly ensuing lymphatic involvement of the cervical lymph nodes undergoing necrosis and ulceration and the formation of draining sinuses, is quite diagnostic

The symptoms will vary depending upon the localization of the infection *There may be considerable dysphagia and inability to ingest* an adequate amount of food The patient may have considerable abdominal pain and severe vomiting The temperature curve at first may not be significant, but as the tissue destruction in the internal organs becomes excessive and secondary pyogenic infection supervenes the fever will become of the septic type Extreme weakness emaciation due to starvation and sepsis may bring about a fatal issue within a few months Cases have been reported to have lived several years and eventually terminate fatally

When the lungs are involved there may be cough with mucopurulent or sanguinopurulent expectoration Rales may be found on physical examination Ordinarily no signs of localized or massive consolidation are elicited The roentgenogram may reveal the diffuse, nodular lesions throughout the lung parenchyma

There are no significant changes noted in the leucocytes until the advent of secondary pyogenic infection Laboratory findings, as the disease progresses are similar to any severe type of septic disease

The diagnosis is comparatively easy to make from the clinical phenomena present and the appearance of the lesions Almeida has de

scribed an intracutaneous test, which may be helpful Smears from the lesions should show the thick walled, round or ovoid, yeastlike cells which are larger than the cells of Blastomyces dermatitidis A characteristic finding is the multiple budding forms noted in the tissues and in cultures

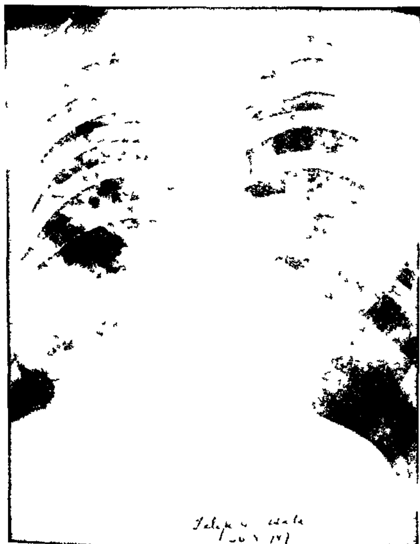


Fig 78 South American blastomycosis

Inoculation of the fungus into the testicles of guinea pigs or the peritoneal cavity of mice will demonstrate the blastomycotic lesions in the mesentery, spleen diaphragm and liver, within approximately six weeks

Complement fixation tests have not been found to be specific as there are cross reactions in chromoblastomycosis epidermophytosis and sporotrichosis

The cutaneous form of South American blastomycosis may be confused with cutaneous leishmaniasis yaws tuberculosis neoplasms and syphilis as well as actinomycosis coccidioidomycosis cryptococcosis histoplasmosis and sporotrichosis The visceral and the lymphatic forms must be differentiated from visceral leishmaniasis syphilis tuberculosis lymphangitis peritonitis neoplasms Hodgkin s disease and leukemia

Iodides are not curative in this disease although it is advisable to administer the potassium iodide in the same manner advocated for the treatment of North American blastomycosis Early cases will show considerable improvement Desensitization of hypersensitive patients should be done in a like manner as is done in North American blastomycosis otherwise the drug may cause widespread dissemination of the fungus The sulfonamides sulfapyridine and sulfadiazine have been reported from South America to be of distinct benefit for a period of time at least Many of the patients so treated succumb eventually to the infection David T Smith has suggested that desensitization with vaccine followed by treatment with sulfonamides might produce more favorable results

COCCIDIOIDOMYCOSIS
(VALLEY FEVER SAN JOAQUIN FEVER COCCIDIOIDAL GRANULOMA)

Coccidioidomycosis is an acute subacute or chronic infection of the lungs caused by the mold Coccidioides immitis acquired usually by inhalation of the chlamydospores of the fungus The disease is ordinarily mild and self limited but exceptionally produces systemic granulomatous lesions with a high mortality Exceptionally the portal of entry may be the skin

The disease is endemic in the San Joaquin Valley of California Arizona the Southwest part of Texas and probably in New Mexico and Mexico It is said to be endemic in the dry Chaco region of South America

Coccidioides immitis has never been found in nature but on one oc

casion Stewart and Meyer isolated the fungus from the soil in an endemic area The organism is diphasic, the infective form occurs in soil and on culture media in the form of hyphae with chlamydospores, in animal tissues as a spherule with a doubly refractile wall These spherules, 10 to 16 micra in diameter, multiply by endosporulation and are found in the sputum, especially if cavitation is present

There is no proof of direct animal to man, or man to man, transmission of the disease Coccidioides immitis has been recovered from the lungs of certain wild rodents in endemic areas, and this fact has led to the supposition that it is primarily a disease of rodents and thence to man Infections in cattle, dogs, and sheep have been reported In spite of the fact that we have no direct proof of transmission of the disease from patient to patient, it has been shown experimentally that spherules or sporangia can be infective through the respiratory route in guinea pigs It has been suggested that active or progressive coccidioidomycosis in human beings should be considered contagious until proved otherwise

Most of the infections are relatively mild and recovery occurs promptly Dark skinned races are especially susceptible to the development of the severe, and usually fatal, granulomatous type of the disease It is true, however, that coccidioidal granuloma is infrequent, in the San Joaquin Valley of California, with a population of 750,000 people, the health bulletins report an average incidence of only 46 cases of coccidioidal granuloma each year

The disease may occur at any age, from infancy to old age, but is most common from the second through the fifth decades of life The sexes are equally affected, but the progressive granulomatous lesion develops most frequently in males

Little is known of the pulmonary pathology of the acute, or subacute types, of coccidioidal infection It is, of course, known that an "acute cold," or bronchopneumonia may develop, and it patently follows the respiratory system will reveal in such patients the commonly known findings in these infections It has been suggested that the bronchial and mediastinal lymph nodes become affected, most likely, in the subacute cases Beck, Traum, and Harrington observed that in infected cattle, the bronchial and mediastinal glands, and these only, were involved Their findings are of note since in human beings, the peribronchial lymph nodes show an old chronic type of lesion contrasting markedly with the more recent lesions It is quite possible these chronically infected hilar

glands constitute foci from which the infection is later disseminated by involvement of the blood vessels It would seem plausible, then, to infer the pulmonary pathology in the more prolonged acute cases would include infection of the hilar lymph nodes, draining the acutely infected lungs, which subsequently clear, leaving the lymph nodes dormantly diseased and localized for years

The granulomatous, progressive, disseminated form of the disease occurs as an endogenous infection, and usually develops relatively soon after the primary infection is acquired Every organ or tissue of the body may become involved, such as the bones and joints, the ribs, pleura, vertebral column skin, meninges, liver, spleen kidneys, heart, and testes The fundamental lesion is granulomatous, acute or chronic, and is associated with varying amounts of fibrosis, superficially these granulomas ulcerate, and may heal, or produce hyperplastic changes Deeper lesions may produce large subcutaneous abscesses with thick, tenacious, yellowish gray pus The lungs may show nodular lesions, thin walled cyst like cavities, hilar glandular enlargement, fibrosed pleural membranes, or pleural effusions. The nodular lesions in the lungs may attain considerable size before necrotic changes occur, however, abscess formation is relatively infrequent

The period of onset of symptoms following exposure to the *Coccidioides immitis* is from 10 to 14 days The early symptoms of the primary phase are those of a mild respiratory infection, with a low grade fever of 99° to 100° F and a moderately dry cough More severely affected patients have higher fever, chills, night sweats, loss of appetite, headache, and backache There may be some blood streaked, mucopurulent sputum, and pleural pain Ordinarily the fibrinous type of pleurisy is noted, although rarely an effusion may be found There may be no physical findings in the chest during the initial phase of coccidioidomycosis, but in some cases depressed breath sounds, dullness, and rales can be elicited The erythematous nodes, ordinarily on the shins, may appear from five days to three weeks, and a concomitant arthritis may develop also at this time Erythema multiforme may appear on the margins of the palms neck, face, and extremities Although this is the usual clinical course of so called "Valley Fever," a variety of pulmonary manifestations have been reported in early coccidioidomycosis, namely, bronchopneumonia and subacute and chronic cavitation resembling tuberculosis It would be fair to say these are among the unusual manifestations, as the primary disease tends to clear in two

to six weeks, and the diagnosis in an endemic area is not difficult. Immunity develops and reinfection does not occur.

The progressively disseminated type, coccidioidal granuloma, may develop directly from the primary form. In some patients there may be no remission of the fever and pathologic changes may appear in the lungs, bones, glands, or subcutaneous tissues, and obviously, the primary phase has evolved into the highly fatal disseminated type. It has heretofore been stated that patients may appear to have recovered from the initial infection, and maintain a dormant, quiescent focus in the hilar glands, and subsequent endogenous dissemination through a blood vessel may result in a severe granulomatous disease. The patients may initially run a continuous low grade fever with productive cough, marked anorexia, loss of strength and weight, shortness of breath and cyanosis. Metastases ensue in the skin, subcutaneous tissues, bones, joints, liver, kidneys, spleen, brain and other organs, and meninges. Smith has stated that the progressive form of coccidioidal granuloma should be suspected if the lung shadows in the primary form persist for more than five or six weeks, and that the diagnosis is almost positive if new lesions appear in the chest, or if tuberculois like infiltrations with clouding mottling fibrosis, or cavitation, appear in the apical or subapical areas. The appearance of joint or bone involvement is, likewise, highly suggestive. If miliary spreading of the infection takes places, the fever becomes high often spike like, frequent chills and drenching sweats, marked weakness prostration and loss of weight follow, and the patient may die within a few weeks.

A negative coccidioidin intradermal reaction generally excludes coccidioidomycosis but it is not always positive when the infection is present, as for instance in disseminated coccidioidomycosis. The foregoing statement bears with it the surmise that a negative test does not rule out a coccidioidal infection. For routine skin tests 0 1 ml of a 1 100 dilution of coccidioidin is used and the test read, together with the control, at 24 and 48 hours. It is generally believed that the longer the skin test remains positive the better the prognosis. It is said by some observers that cross reactions occur with histoplasmin. The value of the skin test is lessened in that its positiveness may indicate a previous mild or undiagnosed infection with Coccidioides immitis.

The most reliable tests are the precipitin and the complement fixation tests. They do not become positive early, as they occur at times three weeks later than the positive skin test. They may be found

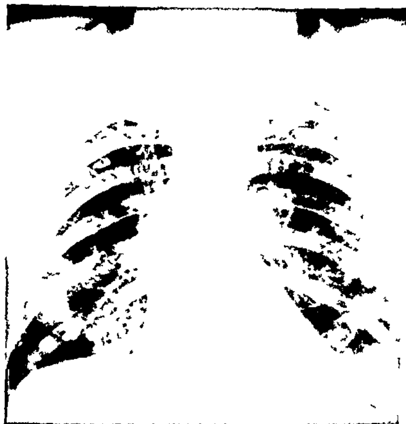


Fig 29 Pulmonary Coccidioidal Granuloma Shows circumscribed nodular lesions in the pulmonary parenchyma and hilar areas (Courtesy Dr W A Winn Springville Calif)

positive in the blood, spinal fluid and chest fluid in the active stages of the disease A negative reaction with either procedure does not rule out the infection The precipitin test is most useful in early stages of the disease, appearing from one week to three months after the initial onset These tests are only positive after allergy is established and in cases in which no anergy exists Smith has shown there is evidence of an irregular cross reaction in histoplasmosis The complement fixation test starts later than the precipitin test and lasts for a longer time—not usually longer than one year in uncomplicated disease The titer of complement fixation increases with the severity of the disease and usually *suggests dissemination*, especially with a negative skin test Titers in excess of 1 to 16 are exceptionally found in non disseminating disease, whereas with titers above 16 systemic dissemination is indicated

Roentgenograms of the chest reveal varying kinds of changes, such as, soft fuzzy hilar thickening, a pneumonic type of infiltration of soft hazy shadows extending from the hilum into the middle or lower lung fields, well circumscribed nodular lesions in the pulmonary parenchyma, mediastinal and hilar glandular enlargement, pleural effusions and cavity formation The roentgen findings in the early stages are non specific, and could be explained by primary atypical pneumonia, rheumatic pneumonitis, bronchopneumonia or tuberculosis The pre dominant roentgen findings in chronic cases have been either nodular parenchymal foci, cyst like cavities persistent pneumonitis, mediastinal and hilar adenopathy, pleural effusion or miliary lung involvement, metastatic bone foci and other evidences of dissemination

When the disease is endemic, and the clinical history of cutaneous or joint lesions suggestive of coccidioidomycosis, the diagnosis may be af firmed by skin testing with coccidioidin, precipitin and complement fixation tests Direct examination of the sputum, stomach contents, pleural fluids and pus, may reveal the Coccidioides immitis as non budding, spherical, thick walled structures, filled with numerous endospores Coccidioidomycosis should be suspected in every puzzling illness, not only in endemic areas, but in localities where the climatic conditions simulate that of the Southwestern part of the United States The primary form may be confused with an acute "cold,' influenza, bronchopneumonia, or primary atypical pneumonia The granulo matous type must be differentiated from tuberculosis, tularemia, syphilis, glanders, osteomyelitis, tumors, blastomycosis, actinomycosis, sporotrichosis, cryptococcosis, and histoplasmosis

The prognosis in the treatment of primary coccidiodomycosis is very good, whereas the results in progressive coccodioidomycosis are poor—the mortality being from 50 to 60 per cent Approximately two-tenths per cent of the total number of patients with coccidioidomycosis develop the progressive, disseminated, granulomatous disease The primary cases usually recover from purely symptomatic treatment

Patients with progressive coccidioidomycosis should be treated along the same lines as any severe illness—general care, adequate diet, iron, vitamins et cetera as there is no specific therapy It is well to test their sensitivity to coccidioidin, and patients highly sensitized should be desensitized by gradually increasing minimal injections of coccidioidin When the desensitization has been accomplished, then, and only then, iodides may be given, as the saturated solution of potassium iodide, be-

tions, bronchitis bronchiectasis abscesses, cavities and fibrosis The clinical picture may be impossible to differentiate from advanced pulmonary tuberculosis

The pulmonary lesion of advanced moniliasis resembles that of tuberculosis with consolidation and concomitant production of strands of fibrous tissue Cavitation is not usually present The microscopic appearance of the lesion resembles tuberculosis, with a central area of caseation surrounded by a zone of lymphocytes and occasional giant cells In asthmatics who develop moniliasis bronchiectasis and emphysema may be found

The appearance of the roentgenogram varies greatly The disease starts in the hilar areas and disseminates outward along the bronchial tree until the entire lung is affected The apices are rarely involved and it is unusual for the process to remain localized in one lung The rule is that the mid and basal regions of both lungs are involved Peribronchial thickening or evidences of bronchiectasis or pneumonic consolidations may be present As the disease becomes more advanced and chronic areas of irregularly spaced fluffy shadows with interbronchial thickening and fibrosis are seen often associated with areas of bronchiectasis and emphysema intervening Cavitation may or may not be present

The diagnosis of bronchopulmonary moniliasis cannot be made solely, from the clinical and roentgenologic findings alone Great care must be exercised in the collection of the sputum for examination it must be obtained directly from the lungs The organism is easily found in the cheesy granules in the sputum The presence of eosinophiles is the rule Animal inoculation should be employed to determine the pathogenicity of the type of Candida found in the sputum The identification of the strain of Candida by biochemical studies on carbohydrate media the differentiation of the species by agglutination intracutaneous testing for hypersensitivity, complement fixation and agglutination tests are all questionable as to their accuracy and dependability

The differential diagnosis must be made from acute pulmonary infections and chronic pulmonary diseases of undetermined etiology Pulmonary tuberculosis which simulates the most severe types must be differentiated

Iodides are almost specific in the treatment of bronchopulmonary moniliasis Potassium iodide should be given in large doses and continued for a number of weeks after all the symptoms have abated Sodium iodide may be administered intravenously, in one gram doses

daily Creosote has been advocated by some Autogenous vaccines may benefit The use of small amounts of immune rabbit serum, injected intracutaneously, has been favorably reported by Hiatt and Martin Farrell has reported a patient, who was cured by five grains of quinine sulphate given three times daily Satisfactory results have been reported from small doses of x rays, and by the giving of sulfapyridine The use of iodides remains the only universally accepted method of therapy Although the most useful therapeutic agents at the present time are the iodides, given orally and parenterally, with or without the use of vaccines, other medicaments have been reported to be beneficial in the treatment of moniliasis Our personal experience with penicillin and the sulfonamides has not been encouraging Streptomycin has been used in conjunction with massive doses of potassium iodide, but it is impossible to state whether streptomycin, alone, would be curative It is our opinion that antibiotics are inert in the treatment of moniliasis Kass has reported the recovery of a patient who received aerosol inhalations of brilliant green in conjunction with iodides and autogenous vaccine therapy He states that one should not use brilliant green in the treatment of fungus infections unless sure that the organism is sensitive to the dye in vitro

SPOROTRICHOSIS

Sporotrichosis is a chronic granulomatous disease, caused by the *Sporotrichum schenckii*, characterized by nodular lesions in the skin, lymphatics and subcutaneous tissues, and occasionally involving the bones muscles joints and, rarely, the lungs and internal organs Although Sporotrichum schenckii is isolated most frequently in America the Sporotrichum beurmanni has been reported abroad

The disease is found generally throughout the United States, but is most prevalent in the North Central States The earliest cases were reported mainly from the Dakotas Kansas, Iowa, Indiana, Ohio, and Pennsylvania Ruediger found over eighty per cent of the cases reported before 1912 had occurred in the Missouri River Valley In Europe most of the reported cases have been from France

The infection is probably due to infected vegetable matter in contact with a minor, localized traumatism It is well known that species of Sporotrichum are common saprophytes found on vegetation throughout the world De Beurmann has shown the disease may be contracted

by eating contaminated fruits and vegetables the infection entering the body through the intestinal mucosa Horses and mules, and particularly rats are susceptible to the infection The disease has been reported to have been contracted from patients having the disease, from cultures, and from rat bite Foerster has reported two cases in which the infection resulted from handling dressings contaminated with Sporotrichum pus The disease may be found from infancy to old age, the average age is about twenty-nine years Males especially laborers farmers, and horticulturists are most frequently affected

The organism is present as spores in the purulent exudate It is seldom seen in fresh preparations but grows well on culture media at room temperature The fungus from cultures is to be observed as a tangled mass of branched mycelium with a large number of pear-shaped conidia present along the course and at the end of the mycelium Rats are particularly valuable as diagnostic aids because of their susceptibility to Sporotrichum infection The inoculation is made intraperitoneally and is followed by peritonitis and pronounced orchitis Sporotrichum schenckii is rarely seen in biopsy section so cultures are essential to establish the diagnosis A mold type of growth is seen on Sabouraud's medium and the tissue stage on cystine blood agar

There are six different clinical types of sporotrichosis namely (1) cutaneous (2) lymphatic (3) disseminated (4) mucosal, (5) skeletal and (6) visceral The pulmonary form of sporotrichosis is quite rare Only six cases were reported by de Beurmann and Gougerot in their book of 1912 Forbes in 1927 stated that the pulmonary form is extremely rare and that visceral lesions of any kind were almost unknown in Sporotrichum infection He is of the opinion that there is little probability of such an infection being a factor in the differential diagnosis of obscure pulmonary conditions

The pathology of pulmonary sporotrichosis as reported by Forbes reveals fibrous adhesions of the pleura so dense that the lobes of the lung are attached securely to one another In areas of the lung tissue many small cavities are seen in what appears to be a honeycomb like structure The cavities are traversed by bands of fibrous tissue not unlike those seen in tuberculous cavities In the walls of the cavities as well as in the consolidated tissues numerous translucent bands of fibrous tissue occur In addition to the cavities there are many scattered gray nodules with yellowish centers each surrounded by semitranslucent connective tissue Similar indurated nodules appear in the grossly normal

lung tissue The nodules are deeply pigmented and dense, giving the affected lung a shotty consistency Thrombosis of pulmonary vessels is seen The bronchi in the indurated, cone shaped areas show scar formation in their walls and marked dilatation The cavities are quite clean, most of them showing only a few flecks of necrotic material The mediastinal and the peribronchial lymph nodes are moderately enlarged The microscopic pathology in the lungs is of three essential types, namely, (1) tubercle formation, (2) cavity formation, and (3) sclerosis

The clinical symptoms of pulmonary sporotrichosis may consist of dyspnoea on exertion, cough with moderate mucoid, occasionally blood streaked, expectoration, with no fever, over a period of several years As the disease gradually progresses, signs of tracheal or bronchial obstruction—inspiratory and expiratory stridor, with wheezing and sibilant rales, may be heard *The roentgenogram reveals shadows extending out*ward from the hilum on each side The cough becomes very severe, the bronchial obstruction increases, and the patient succumbs

The agglutination reaction is of diagnostic value, although cross re actions occur with actinomycosis and thrush Skin testing is of less value than the agglutination reactions Complement fixation tests are of more value Isolation of the fungus in culture, and inoculation of a rat, are the best diagnostic procedures

The clinical appearance of the cutaneous and the lymphatic forms of sporotrichosis is so characteristic that the diagnosis is easily made They must be differentiated from tuberculosis, syphilis, pyogenic in fections, leprosy, glanders, tularemia, and various mycoses, notably coccidioidal granuloma and North and South American blastomycosis

The number of primary lung conditions to be differentiated from pure pulmonary sporotrichosis are few, and aspergillosis, blastomycosis, *coccidioidomycosis, syphilis, and tuberculosis may be mentioned*

The prognosis is excellent except in the fulminating disseminated form, cases with involvement of the mucous membranes of the throat and larynx, and the pulmonary form

The treatment in the late pulmonary form is obviously of little bene fit Since potassium iodide is almost a specific in the treatment of sporotrichosis, it is likely, if the disease were recognized early, that treatment might be successful The iodides should be given in rapidly increasing dosage, beginning with 10 drops of the saturated solution three times a day, and increasing 5 drops daily, until the patient is receiving 40 or 50 drops thrice daily If any digestive disturbance ensues from the oral ad-

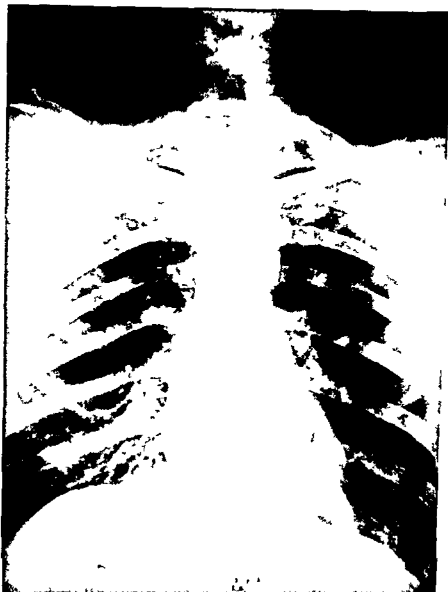


Fig 31 Pulmonary Sporotrichosis Shadows extending laterally and basally outward from the hilum on each side with considerable peribronchial thickening and many small to medium sized round translucent areas

ministration of the iodides sodium iodide in 15 grain doses may be given intravenously each day If there are any open lesions, they should be irrigated with an aqueous iodine solution

Surgery may be indicated for incision curettage, or excision of the lesions X ray therapy may be tried either with or without surgery Vaccines preferably autogenous may be used as a supplemental treatment

HISTOPLASMOSIS
(RETICULO ENDOTHELIAL CYTOMYCOSIS)

Histoplasmosis is a disease of the reticulo-endothelial system caused by the fungus Histoplasma capsulatum The disease first described by Darling in 1906, was characterized by irregular fever emaciation leucopenia anemia and splenomegaly It has been observed more recently that papular and ulcerative lesions occur in the mucous membranes of the intestines nose and mouth as well as enlargement of the liver and lymph nodes

Darling was of the opinion that the organism was a protozoon Rocha Lima in 1912 concluded that Histoplasma capsulatum was a fungus It has been suggested that domestic pets may be carriers of the disease The disease is pathogenic for rabbits guinea pigs mice rats and monkeys The age of incidence varies widely being from three months to 70 years The organism is supposed to enter the body through the oral cavity and the intestines Lesions are frequently found about the mouth and nose The lungs have been reported to be affected in 20 per cent of the cases The disease is widely spread throughout the world cases having been reported from Central and South America the United States Java Africa and Europe and the Philippine Islands

Efforts to culture the organism were not reported until Hansmann and Schenken published in 1934 their success in cultivating the fungus from biopsies of the skin inguinal lymph nodes and buccal mucous membrane They reported their case as a new disease caused by a yeast like fungus interpreted by them to belong to the genus Sepedonium of the Fungi Imperfecti De Monbreum in 1934 studied the fungus obtained from blood cultures taken two days before death and of the spleen at autopsy and described the fungus as Histoplasma capsulatum of Darling A few years later de Monbreum isolated the fungus from a dog and was of the opinion this fungus should be considered a member of the Fungi Imperfecti

The fungus is characterized on culture by two phases a saprophytic and a parasitic phase The saprophytic form is seen as a filamentous loose cottony whitish to light brown mycelium producing small and large unicellular smooth to nodular chlamydospores in cultures at room temperature and small budding yeastlike cells on blood agar at

37° C This latter small budding form is the parasitic type and causes the fatal disseminated infection in dogs and in man Yeastlike oval bodies phagocytized by endothelial leucocytes are to be found in the infected tissues The use of the Hotchkiss McManus staining technique demonstrates vividly the yeastlike bodies in the mononuclear cells of the stained tissues *Giemsa and hematoxylin eosin stains are likewise* serviceable The fungus grows well on blood agar and Sabouraud's media *It* is well to remember when culturing sputum to mix penicillin and streptomycin with the material to be examined to a final concentration of 1000 units of each antibiotic per cc to suppress the growth of common bacterial contaminants *Christie and others have advised* the addition of 5 per cent human plasma to culture media as well as the inclusion of penicillin and streptomycin as supporting agents

The general tissue reaction to the fungus is the formation of small white or grayish white nodules disseminated throught the affected viscera These nodules may coalesce, undergo central necrosis and form areas of yellowish powdery or mealy material *The histologic appearance* of a necrotic nodule is not unlike tuberculosis showing a central area of necrosis surrounded by moderate proliferation of fibroblasts and *large infiltration of mononuclear cells These mononuclear* cells are filled with the organisms which are round or ovoid and from three to five microns in diameter With hematoxylin or Giemsa's stain one sees the fungus as an intensely stained gram positive central area surrounded by a clear zone and a refractile capsule The lungs almost always affected in the disseminated cases show hilar adenopathy *and small sub*pleural or pleural nodules There may be ulceration in alveoli Gray or white nodules with considerable necrosis and cavitation have been encountered The pleura frequently shows a recent fibropurulent or ganizing process or dense fibrous adhesions

The roentgenogram of the chest in the opinion of many observers is important in *differentiating histoplasmosis from tuberculosis Gross* hilar adenopathy associated with disseminated nodular pulmonary lesions is usually present The mediastinal changes are distinctive in the considerable degree of glandular enlargement Arblaster considers this finding typical of histoplasmosis Furculow has noted multiple foci in the parenchymal lung tissue which are mostly discrete but coalesce in areas to form raspberry like opacities Calcifications if present have a halo like zone seeming to surround the calcification which is now *believed to be a part of the calcification itself* The two features, gross

hilar adenopathy and halo calcifications, are highly suggestive of the diagnosis of histoplasmosis

The clinical symptoms may very widely Four types of histoplasmosis have been observed (1) a picture with a septic temperature curve, anemia, leucopenia, enlarged liver, and spleen, simulating kala azar, (2) with predominating lymph adenopathy, similar to leukemia, aplastic anemia, Hodgkin's disease, or lymphosarcoma, (3) with pulmonary symptoms predominating, often superimposed or complicated by tuberculosis, (4) with a primary, small cutaneous lesion, which may develop into a generalized ulcerative skin disease The fact that there is such a widespread variety of clinical manifestations of histoplasmosis suggests the possibility that benign forms may exist The reports of numerous observers, including Palmer, on nontuberculus complications of the lungs, and sensitivity to histoplasmin skin tests, makes the assumption decidedly plausible It seems reasonable to infer that a positive reactor to histoplasmin had a previous infection with the fungus, when we grant the same specificity to the histoplasmin test as is commonly recognized for other intradermal tests, such as testing with coccidioidin and tuberculin The problem of the existence of a benign type of histoplasmosis depends upon a similar specific relationship between positive reaction to histoplasmin and the infection It is widely believed that a great number of pulmonary calcifications observed in the roentgenograms of tuberculin negative persons might be due to histoplasmosis and not to tuberculosis It seems that histoplasmosis may exist, especially in the Eastern Central part of the United States, in a benign form in persons with pulmonary calcifications, who are negative reactors to tuberculin and coccidioidin

The finding of intracellular round, or oval, yeastlike fungi in mononuclear cells from smears or cultures of the peripheral blood, bone marrow, sputum, lymph nodes, or other biopsy material, or splenic pulp, is diagnostic Infected matter, injected intraperitoneally, into mice and guinea pigs should reveal the organism

Medical literature in recent years has been replete with studies dealing with the value of positive histoplasmin sensitivity tests in negative tuberculin reactors in evaluating the etiology of benign pulmonary calcification Palmer, Christie, Peterson, Furculow and many others have shown that a high rate of histoplasma infection has been attained by the time of adolescence within the endemic areas reaching from the western slope of the Appalachian Mountains to and



Fig 32 Pulmonary Histoplasmosis Homogenous density in lower two thirds of right lung field at left base a band of density extending to pleura with irregular fine infiltrations above old calcified nodules in both lung fields and calcification in hilar areas (Courtesy Dr H E Meleney New York University College of Medicine New York)

including the states bordering the Mississippi River Our allotted space will not permit a detailed recital of their studies It is sufficient to affirm that their researches have proved their contention that there are within this endemic area thousands of patients with pulmonary calcifications due solely to previous benign histoplasma infections The problem is more complicated in studying pulmonary calcification in nonendemic areas because of cross reactions with two other fungi Coccidioides and Blastomyces The recent studies of Emmons *et al* have raised doubt upon the specificity of the histoplasmin test in that they found a marked degree of cross reactions with histoplasmin in heterologous fungus infections Howell and others have demonstrated

that different lots of histoplasmin vary markedly in their critical titers, and that good antigens yielded very few cross reactions The need for improving and standardizing histoplasmin preparations is evident

The exact significance of the histoplasmin complement fixation tests awaits further observation and experience It may be stated at this time that negative serological studies do not rule out histoplasma as the etiological agent It would seem logical to infer that the histoplasmin complement fixation test has a similar relationship to histoplasmosis that the coccidioidin complement fixation has in coccidioidomycosis This would indicate possibly an absence of the histoplasmin complement fixation test in early as well as regressive coccidioidomycosis, and furthermore, the appearance of a positive serology would suggest the likelihood of dissemination of the disease In such cases the skin test might become negative with the appearance of a strongly positive complement fixation reaction

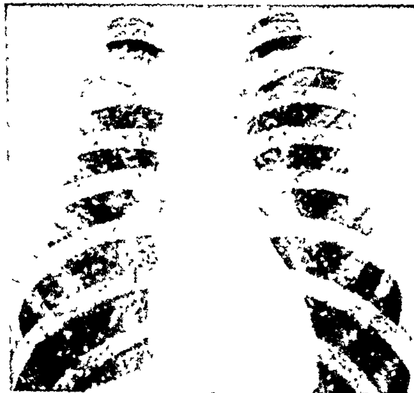


Fig 33 Pulmonary Histoplasmosis

Histoplasmosis must be differentiated from cutaneous and ized leishmaniasis, syphilis, tuberculosis, tularemia, Vincent's sporotrichosis, actinomycosis, North and South American blastom moniliasis, toxoplasmosis, coccidioidal granuloma, leukemia, Ho disease, lymphosarcoma, malaria, Banti's disease, infectious m cleosis, agranulocytic angina, Gaucher's disease, tuberculous per and amebiasis

The prognosis in the disseminated types was formerly beli be 100 per cent fatal but in recent years a number of authentic eries have been reported The presence of a benign form, a gested by its rather general recognition, would lead us to the assur that there is a mild type of histoplasmosis which recovers spontane

Treatment in disseminated histoplasmosis has been ineffectua the past few years The use of iodides, x ray, liver and bone m extracts, iodized metals, pentnucleotides arsenicals and sulfona has resulted in failures Antibiotics, including streptomycin, have of no benefit The aromatic diamidines of which stilbamidine has used more extensively have been advocated in the treatment of plasmosis Patients treated with stilbamidine have shown early imp ment in some instances but the benefit is not sustained Christi his associates have advocated the use of ethyl vanillate—the ethyl of vanillic acid, and report recoveries in 5 of 12 children with plasmosis of the progressive and disseminated type They state vanillate is difficult to administer, the level between therapeutic toxic levels is only 25 to 30 per cent, a margin of safety too small desirable therapeutic agent

CRYPTOCOCCOSIS
(EUROPEAN BLASTOMYCOSIS, BUSSE BUSCHKE'S DISEAS

Cryptococcosis is a subacute or chronic infection, caused by Cryptococcus neoformans, affecting particularly the central nervous tem, the lungs secondarily or disseminating to any tissue of the bod

The genus Cryptococcus was first described by Kutzing in 1833, *Dodge states it is quite likely the genus name, Cryptococcus,* has confused with an imperfect yeast from the intestinal tract or an a parasite of domestic animals Vuillemin, in 1901, again established genus Cryptococcus for the nonspore-producing, nonfermenting ye from animal substrata

Although there are two main pathogenic types of Cryptococcus are concerned with only one, the *Cryptococcus neoformans.* The o

group is found in certain kinds of tumors and was intensively studied at the time the yeast theory of cancer was an outstanding idea

The fungi are characterized as spherical, ellipsoid or ovoid cells occurring singly or in irregular groups which are held together by the secretion of thick, jelly like capsules They do not form endospores nor is a mycelium present On liquid media a thick membrane or pellicle develops by the merging of slimy, floating islands The fungus does not ferment and rarely produces acid on sugars

Cryptococcosis has been reported from Europe North and South America, and the Southwest Pacific area The disease is not transmitted from man to man nor from animal to man It is probable that the atrium of the infection is through the respiratory tract because primary cryptococcosis is not rare and a history of initial respiratory symptoms is frequently obtained in the severe types of the disease, such as cryptococcal meningitis It is probable the lesions in the central nervous system are embolic phenomena and dissemination is by the blood stream The infection may occur at any age, but is most commonly found in the 40- to 60-year age group Males are about twice as susceptible as females The cryptococcus fungus is widely distributed in nature It is likely that all types of cryptococci are originally nonpathogenic but may become pathogenic under suitable conditions

The lungs are involved in forty per cent of the cerebrospinal forms of cryptococcosis There is a pronounced inflammatory reaction in the pulmonary tissues likely due to the great amount of mesodermal tissue present Miliary lesions may be present throughout the lungs Cavitation is rare The mediastinum is practically never involved The cerebrospinal types show at autopsy a granulomatous meningitis most marked at the base The subarachnoid and ventricular fluids are turbid at times slimy and gelatinous There may be an involvment of the cerebral cortex of either cystic or granulomatous lesions associated with varying degrees of inflammatory infiltration The organisms are usually abundantly present

The clinical symptoms of the pulmonary form are not characteristic There is usually a low grade fever slight dry occasionally productive cough The location of the pulmonary lesions varies and may develop in any part of the lungs The physical signs are not of diagnostic importance, as ordinarily only altered breath sounds and dullness are present Rales are inconstantly present except in patients having a widespread miliary dissemination throughout the lungs

A striking fact in the clinical course of the disease is its chronicity and the fluctuations in symptomatology. Freeman has summarized the clinical features of the cerebrospinal form as follows: the onset is accompanied by headache that becomes progressively more persistent and severe, associated with pain and stiffness of the neck, pain in the limbs and nausea and vomiting. Disturbances in sleep, amblyopia and diplopia are next most common, and mental phenomena suggestive of organic disease of the brain may follow. The syndrome occurs in an individual whose bodily functions are not otherwise upset and suggests some primary disturbance in the central nervous system, either chronic meningitis, atypical epidemic encephalitis or unlocalized neoplasm.

The roentgenogram of the lungs frequently shows dense and large shadows with no cavitation and no enlargement of the mediastinal areas. In terminal cases widespread miliary nodules may be seen throughout both lung fields.

The laboratory examination of the blood, either cellular or chemical, may reveal nothing of note. The sedimentation rate is increased. When the meningeal form is present, as is usually the case, the spinal fluid is increased, may be clear, turbid or xanthochromic. The cell count is moderately increased. Globulin and albumin are increased, the sugar is generally decreased but may be normal. The organisms may be found in the spinal fluid by direct smear and by culture.

The differential diagnosis is made by finding the Cryptococcus neoformans in the lesions. Pulmonary cryptococcosis may be confused with other types of pulmonary mycoses, tuberculosis and syphilis. The fact that the mediastinum is rarely invaded in cryptococcosis is important diagnostically in differentiating it from pulmonary actinomycosis, North American blastomycosis and coccidioidomycosis.

The prognosis in cryptococcosis is very grave, and few recoveries has been reported. The average duration of life is only three and one half months. It is possible that only the severe forms of the disease have been reported, and there might exist a mild, unrecognized form.

The treatment has been ineffectual. Iodides and other chemotherapeutic agents have been of no avail. There is some evidence that sulfonamides may be of some benefit as is indicated by the use of sulfadiazine in Marshall and Teed's case. Several agents have been found to be of benefit in the treatment of those cases without meningeal involvement, with the iodides, sulfadiazine and protoanemonin being credited with cures of the lung and other lesions of cryptococcosis.



Fig 31 Pulmonary Cryptococcosis (After iodized oil) Dense enlarged shadows without cavitation

The use of vaccines has been disappointing Seegal noted the inhibiting effect of elevated temperature in the growth of Cryptococcus neoformans, and that the action of actidione was potentiated by elevated temperatures in vitro It is likely that there is a fairly good basis for

the use of fever in the treatment of cryptococcosis as an adjuvant form of therapy Several reports concerning an antifungal agent isolated from the Bacillus subtilis have suggested its use in the local chemotherapy of fungous diseases, among these agents, which possess fungistatic and fungicidal properties in vitro, are antibiotic XG and mycosubtilin It is possible they might have a place in the local therapy of cryptococcosis and other fungous diseases as well They have not been tried against human central nervous system infections with C neoformans, but if more purified and less toxic products become available clinical trial would be warranted Extensive laboratory investigations in the study of antibiotic agents against the Cryptococci by Klingman and Weidman may be summarized by stating that actidione, bacillomycin B, allein, pleurotin, protoanemonin, tomatin and eumycin have varying degrees of activity in vitro

Actidione was reported in 1945 by Waksman, Schatz and Reilly as a second antibiotic while working with Streptomyces griseus in the preparation of streptomycin Hellstrom noted antifungal activity of actidione for a variety of fungi, and particularly for C neoformans Actidione has been used in doses ranging from 10 mg, twice a day to 30 mg, four times a day by the intramuscular route, intravenously in doses as high as 180 mg per day, and intrathecally in doses of 4.5 and 10 mg per day It has also, been administered intraventricularly in doses of 20 to 30 mg per day The drug appeared to affect favorably the fever curve in several patients, associated with slight clinical improvement The toxic effects consisted of nausea and vomiting seemingly of central origin, and severe shooting pains in both legs and buttocks At least two cases of low grade meningeal infection with cryptococcosis have been favorably influenced by a course of intrathecal actidione, and Wilson and Duryea have reported a case of cryptococcic meningitis apparently cured with actidione It is possible the future may bring this almost universally fatal disease some degree of hope It would seem the use of vaccine therapy, fever therapy, protoanemonin B subtilis derivatives and actidione might suggest avenues for approach to the problem

ASPERGILLOSIS

Aspergillosis is an acute or chonic infection of the lungs, caused by the Aspergillus fumigatus, characterized by either an acute course, simulating acute bronchopneumonia, or a chronic course, similar to fibroid pulmonary tuberculosis

The disease is common in domesticated birds, chickens, ducks, and pigeons, which, in such instance, can be traced to eating moldy grain Cattle, horses, and sheep, have been reported to become infected by eating infected hay or grain or by the inhalation of vegetable material The pulmonary form of aspergillosis is not common in man, and although the disease is not limited to geographical distribution, most of the cases have been reported from France and Germany The disease, either as the primary or the secondary form, is found in America, the author having observed both forms of the disease in South Texas There is a tendency to the development of aspergillosis in regions of high humidity

Occupation as a predisposing factor is important Breeders and handlers of pigeons are likely to become infected, and, to a lesser extent, persons exposed to dust from grain and hair sorters, who use rye flour in large quantities One of my patients was a baker, who specialized in making rye bread The disease may occur at any age or in any sex It may complicate a previously existing pulmonary disease, such as pulmonary tuberculosis, chronic bronchitis, or bronchiectasis

A wide variety of the Aspergillus genus have been reported to have some pathogenic qualities, but the Aspergillus fumigatus is generally recognized to be the most pathogenic species Dodge lists eight species of Aspergillus, namely, Aspergillus giganteus, mencieri, bronchialis, fumigatus, minimus, Brodeni, Vanacampenhouti, and cyaneus, which have been isolated in bronchial and pulmonary diseases of man He states the Aspergillus fumigatus is the most common species isolated from cases clinically resembling pulmonary tuberculosis

The organism, as seen microscopically, is made up of a stalk or aerial hypha, enlarging toward the top with flask shaped vesicles in which are attached chains of conidia, lying approximately parallel to the axis of the stalk The conidia in this manner produce a hemispherical, cylindrical, globose, or elliptical head attached to the perpendicular stalk The fungus grows well on all laboratory media at room temperature

Two types of aspergillosis are seen clinically in man, the acute, similar in appearance to acute bronchopnuemonia, and a chronic type, simulating chronic pulmonary tuberculosis The symptoms of the acute form may be very severe, with cough, fever, prostration night sweats, and signs of great toxicity The physical signs are those elicited in ordinary acute bronchopneumonia The onset of the chronic type is insidious, the ensuing symptoms consisting of loss of weight and strength, cough

with expectoration of mucopurulent, often blood tinged sputum, slight fever, anorexia, and night sweats. The loss of weight is ordinarily slight and some patients appear healthy and moderately vigorous, although tiring easily Frequently, a diagnosis of pulmonary tuberculosis is made and the patient is confined to his bed More usually however, the patient may continue his vocation at a reduced level of activity A common symptom is recurring hemoptyses, which may be of considerable quantity of blood The sputum may contain at irregular intervals, tangled nodules of fungus filaments from which the organism may be readily seen by direct smears The physical findings simulate pulmonary tuberculosis to a degree only We have never elicited signs of massive dullness nor cavitation The breath sounds are usually somewhat harsh and rales are inconstantly found The radiographic findings are similar to those of chronic pulmonary tuberculosis

Recent reports of the development of pulmonary aspergillosis have appeared in medical literature following the administration of antibiotics for upper respiratory infections, or for post influenzal bronchopneumonia It has been suggested that suppression of bacteria usually competing for food with the coexisting fungus infection is probably the most important factor in the development of these infections

Pathologically, gray or greenish gray necrotic areas of the bronchial mucosa and of the lung tissue, surrounded by other cellular elements in different stages of degeneration are found The lung shows more or less diffuse chronic infiltration around these areas The necrotic areas usually communicate with the lumen of the bronchi Numerous mycelia spores, and fine mycelial filaments may be seen in the parenchyma and within the lumina of cavities and blood vessels Foci of hemorrhagic alveolar exudate may be found, and occasionally a few alveoli containing cellular debris are seen in the center of these lesions Monocytic and plasma cell infiltration and an occasional multinucleated giant cell may be noted at the periphery of these lesions A perivascular exudate of round and plasma cells, as well as a like infiltration of the bronchial walls with these cells, may be seen

Primary pulmonary aspergillosis should be differentiated from pulmonary tuberculosis bronchitis, and bronchopneuomnia

Specific cutaneous hypersensitivity to the fungus antigen is the rule the local reaction appearing in 24 hours, and resembling the tuberculin reaction closely Agglutinins and complement fixing bodies have not

been noted with any constancy Inoculation of the infected material or culture into the lung of a rabbit will produce pathological pulmonary changes, from which the fungus can be isolated within a period of two weeks



Fig 35 Pulmonary Aspergillosis Massive irregularly shaped calcifications seen in both hilar areas with medium sized calcifications scattered throughout right basal area hazy infiltrations left base marked fibrosis left pleura

The prognosis as to mortality is excellent, but as to eradication of the infection in the chronic type is poor

The treatment is not very effectual Iodides by mouth as the potassium salt, sodium iodide intravenously, ethyl iodide inhalation, and autogenous vaccines may be beneficial We have seen best results in ameliorating the cough and expectoration by giving the autogenous vaccine for prolonged periods by the intradermal method, supplemented by

iodized oil injection into the bronchial tree In our hands, the use of iodides by mouth has been valueless

GEOTRICHOSIS

Geotrichosis is a rare, mycotic infection, caused by the genus Geotrichum, usually affecting the respiratory and intestinal tract, and ordinarily characterized by a mild clinical course

The type species is Geotrichum candidum Link, and was first reported in 1809 The cytology of only one species, Geotrichum versiforme, has been carefully investigated by Moore There is a true mycelium, whose hyphae elongate, with septate formation proceding rapidly, until uninuclear arthrospores develop Blastospores may be produced on certain media, but ordinarily, they are not present The conidia are densely filled with protoplasmic material, but no nucleus is present In liquid media a firm, white, resilient mass is found, on solid media the growth is at first firmly adherent, later becoming soft and creamy

There is some confusion in regard to nomenclature in that Geotrichum candidum is frequently known as Oidium lactis, or Oospora lactis Henrici is of the opinion this is incorrect, and that Oidium lactis has only a slight resemblance to Geotrichum candidum The genus is quite large, most of the species being saprophytic on earth and decaying organic matter, as well as in the mouth and gastrointestinal tract Although the infection is usually endogenous, cases of exogenous infection of the skin have been reported The Geotrichum may be found concomitantly with other infections, such as blastomycosis, enteritis, pulmonary abscess, and bronchiectasis

Dodge stated, in 1935, that thirteen different genera had been reported in man, eight from infections of the respiratory tract, three from stools, and two from blastomycosis

Little is known about the pathology of bronchial and pulmonary geotrichosis because of the mild course of the infection

There are four forms of geotrichosis, oral, intestinal, and bronchial and pulmonary parenchymal types of the disease The most frequently recognized manifestation is the bronchial one in which the patient has a persistent cough and expectoration of a characteristic type of sputum The sputum is mucoid or gelatinous, white in color, occasionally blood streaked, containing grayish flakes, and has a yeasty odor Ordinarily there is slight or no elevation of temperature and the general health of the patient is not materially affected The peculiar type of gelatinous

mucoid sputum should lead one to suspect the disease, especially if found in cases of ill defined etiology The physical signs are not distinctive, consisting of scattered, coarse rales, heard particularly in the basal



Fig 36 Pulmonary Geotrichosis An extensive disseminated bilateral patchy infiltrative process which seems to be progressive (Courtesy Dr Ralph H Kunstadter, Chicago, Illinois)

areas of the lungs In the roentgenogram there may be seen generalized peribronchial thickening, and occasionally a fine mottling in the lower portions of the lungs The pulmonary form of geotrichosis is not unlike pulmonary tuberculosis The symptoms of the pulmonary form consist of cough fever, increased pulse and respiration, and increased white cell count The sputum is of a more mucopurulent character than in the bronchial form and lighter than the greenish mucopurulent sputum of tuberculosis The roentgenograms show homogenous dense areas of infiltration and thin walled cavities may be seen in any part of the lungs

The organisms as found by direct examination of the sputum or by culture are seen as rectangular or oblong cells with square or rounded ends It is possible to mistake the rounded somewhat thick walled cells found in cultures, for the budding forms of Blastomyces dermatitidis but if the slides are studied carefully for the presence of the rectangular cells which are not found in North American blastomycosis differentiation can be made It is important to differentiate geotrichosis from North American blastomycosis, because in the latter the prognosis is exceedingly grave whereas in the former, the prognosis is good with the proper treatment The disease must be differentiated from pulmonary tuberculosis coccidioidomyosis cryptococcosis moniliasis and chronic bacterial infections

The diagnosis of geotrichosis should be suspected as heretofore stated in patients with ill defined symptoms and who have the peculiar type of gelatinous mucoid sputum characteristic of geotrichosis

The therapy consists of the administration of potassium iodide by the rapid method The pulmonary type of patient should be confined to bed given general dietary medicinal and supportive treatment It is to be stressed that the presence of a tuberculous infection be entirely eliminated before iodides are given Autogenous vaccine has been advocated and may be given with benefit in conjunction with the administration of iodides

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CHAPTER VI

PULMONARY MANIFESTATIONS OF SYSTEMIC INFECTIONS AND INFECTIOUS DISEASES

SARCOIDOSIS

By J J SINGER M D

SARCOIDOSIS was *originally recognized as a cutaneous condition* it is now known to be systemic The skin is still the most frequently recorded site of sarcoid lesions perhaps because sarcoidosis without skin lesions is so easily overlooked Pulmonary lesions have been found in about ninety per cent of the instances reported In the great majority of patients lymph nodes, both superficial and deep are found to be enlarged Mediastinal nodes are oftentimes massive All organs of the body are subject to the disease with spleen liver, intestinal tract and kidneys involved with some frequency Bones may also be affected—particularly the small and long bones of the extremities A characteristic of the disease, as pointed out by Rich and others, is an unusual tendency to involvement of the heart particularly the myocardium There is no pattern of involvement which may be fairly limited or include almost every tissue of the body As Pinner indicated sarcoidosis is probably the basic condition in many syndromes previously described as etiological entities

Etiology

Apparently most investigators now believe that sarcoidosis is a non caseating tuberculosis, although Rich, as late as 1944, felt the evidence for a tuberculous etiology unconvincing The basic facts that need to be considered in an etiological discussion are these (1) The sarcoid lesion is microscopically and macroscopically very much like a highly productive but non exudative, tubercle (2) In the great majority of *sarcoid lesions tested by various means acid fast bacilli* have not been demonstrable (3) Reaction to tuberculin is invariably negative or slightly positive (4) Distribution of lesions is convincing evidence for the concept of the pathogen as blood borne (5) Frank and fulminating tuberculosis is the terminal event in from ten to twenty per cent of

all patients with diagnosed sarcoidosis—more than any suggested non tuberculous etiology reasonably accounts for

There is some evidence for the suggestions that acid fact bacilli of low virulence are responsible for the non typical reactions observed in sarcoidosis Pinner was able to find seventeen cases of sarcoidosis in which acid fact bacilli were demonstrable by animal inoculation, in all instances the development of tuberculosis in the injected animal was quite slow However the typical highly virulent tuberculosis that sometimes terminates sarcoidosis mitigates against this explanation It seems more likely that the factor responsible for this slow development is the very small number of acid fast bacilli or acid fast bacilli that have been inhibited by the sarcoidosis process in the human patient Some confirmation for this view is found in the same series of successful inoculation. In two instances repeated animal passage tended to produce typical tuberculosis

The most convincing explanation of the etiology of sarcoidosis to the author is that the disease represents an abnormal reaction by a host to ordinary tubercle bacilli Further there is a strong implication in the published reports that the disease is a reinfection phenomenon Even in the necessarily abbreviated form in which Rubin and Pinner give their summaries of twenty five necropsies there is really a suggestion of previous tuberculous infection—a history of close contact of positive tuberculin reaction at some point of calcified mediastinal nodes or parenchymal lesions In view of this the characteristically negative response of the victim of sarcoidosis to tuberculin is not an argument against tuberculous origin A sizable percentage of patients with sarcoidosis would normally have positive reactions if the disease itself did not in some way inhibit hypersensitivity A careful search in future autopsies for primary tuberculous lesions and an attempt in reporting such autopsies to distinguish between old tuberculous lesions and sarcoids should clarify this possibility

The appearance of new sarcoids in the patient over a long period suggests an internal focus from which the pathogen is disseminated We believe that ruptured tuberculous focus emptying into the blood stream best accounts for the peculiar findings that are continually reported in the disease This explanation would account for the occasional instances in which acid fast bacilli are isolated in a patient s sputum or gastric washings once in numerous attempts It accounts for the not infrequent disappearance of the sarcoid involvement as well as the termi

nal tuberculosis that is also not infrequent No other explanation accounts so readily for the instance reported by Bergmann, in which the patient developed terminal tuberculosis of the bovine type

This etiology also accounts for the confusing reports of acid fast bacilli present or absent in the sarcoid lesions themselves Kyrle found scattered acid fast bacilli in very young sarcoids, these disappeared as the lesions matured If we predicate small amounts of bacilli distributed by the bloodstream we should expect initial proliferation at the site of deposition and a productive response The sarcoidosis patient, however, does not respond typically to such bacilli—exudation and necrosis (known to be related to hypersensitiveness) do not occur It is not surprising in such instance that the bacilli are overcome, so as to be difficult or impossible to demonstrate, by the phagocytosis and productive response unimpeded by exudation It is commonplace observation in tuberculosis that the more exudation the more acid fast bacilli and that they are sometimes difficult to demonstrate in tubercles that are predominantly productive

The production of sarcoids at the site of various injections in patients with sarcoidosis is also readily accounted for, any injected foreign substance *would be a point of accumulation of the acid fast* bacilli The finding of an occasional sarcoid in patients without sarcoidosis as reported by Pinner, might well be explained as a patient with the sarcoid reaction to acid fast bacilli who was only accidently exposed to them Regressions and exacerbations, which incidentally seem to coincide with rest and activity in many instances, would depend upon the deposition of bacilli in the bloodstream

The best evidence for the foregoing view of the etiology of sarcoidosis is found in the experiments of Warfvinge in which typical sarcoids were produced upon patients with sarcoidosis by the injection of killed tubercle bacilli Further confirmation is found in the woman he reports to *have both pulmonary tuberculosis and sarcoidosis*—the tuberculosis presumably releasing bacteria into the blood stream with the sarcoidosis reaction prevailing in other parts of the body

No other explanation of the etiology of sarcoidosis fits so well the multitudes of manifestations reported The recent article by Tornell by itself would suggest a fungus infection but when it is integrated with other findings this etiology becomes considerably less than convincing—particularly since Monilia, the suspected fungus, has non pathogenic forms

The classification of sarcoidosis as "of tuberculous origin" does not, of course provide a complete answer to the etiology of the disease The question remains as to why a few persons only should manifest such a distinctive reaction to acid fast bacilli There is little information even bearing upon this question The typical changes in blood if they could be demonstrated to be present, might suggest a basic abnormality In the absence of such a demonstration the question remains an open one

Pathology

The sarcoid begins in soft tissue as a small area of inflammation Langhans cells are found in most instances Masses of reticulum fibers are characteristic of old lesions Necrosis does not take place to an appreciable degree

Sarcoids are small round and sharply defined Development is slow When they are subcutaneous they range from a dark red to a brown or purple. An old sarcoid may be quite yellow When they do not lie on the surface of an organ they are hard rubbery and spheroid

Resolution of the lesion may be by resorption Cutaneous sarcoids disappear very slowly but in internal organs as seen by roentgen ray they may disappear in a period of a few weeks The commonest termination is fibrosis in which the lesion is replaced by scar tissue As Pinner points out, this fibrosis is ordinarily much coarser than that of tuberculosis

As remarked the lungs are involved in most cases of sarcoidosis The involvement may be extensive and progressive The hilar lymph nodes will almost always be involved at one stage or another although the disease process here may be regressive The basic manifestation of sarcoidosis of the lungs is a rather dense seeding of both lungs heaviest in the bases and around the hila Instances of regression and clearing do occur, but they seem exceptional Ordinarily the development is to fibrotic replacement of the sarcoids with thickening of arterial walls and linear, non-specific fibrosis a not uncommon development Occasionally, dry, heavily fibrosed cavities are found at autopsy, which may be a product of sarcoidosis but which are more apt to result from an earlier tuberculosis

The course of the disease is usually lengthy with a five year survival not uncommon Long periods of remission are frequently found with the disease process apparently permanently arrested in many instances Death of the patient due to sarcoidosis itself is not the usual finding It

may occur simply because of massive lung fibrosis which fatally limits function, or causes right-sided heart failure It may also cause the death of the patient by lesions in glands essential to life, or by interference with vital function by the location of a single or several sarcoids As discussed under etiology, widespread and uncontrollable tuberculosis is reported as the terminal event sufficiently often to indicate an etiological connection

As mentioned in the introduction, all organs may be the site of sarcoids A generalized adenopathy is very common Multiple or discrete sarcoids of the skin of the face and extremities is the most characteristic and suggestive finding, but it is not infallibly present and so not an absolute criterion for diagnosis

Clinical Symptoms

Sarcoidosis may present an extensive involvement with no clinical symptoms at all When symptoms are present they are often the result of mechanical interference with organ function by the sarcoids Intestinal dysfunction because of obstruction, or impaired kidney function, is common Severe dysfunction may occur if sarcoids are situated on the adrenals

The most common generalized symptoms are loss of weight and strength A low grade fever is sometimes encountered but it is never a striking feature of the disease process itself

Involvement of the lung may, as indicated, lead to dyspnea of great severity Such a development is seldom found as a presenting symptom Mild dyspnea upon exertion is very common Instances of encroachment of enlarged mediastinal nodes upon the trachea or major bronchi have been reported

Physical Signs

In most patients with sarcoidosis, the typical skin lesions will be obvious Where they are not visible, small firm nodules are sometimes noted on palpation Enlarged lymph nodes can often be palpated and in some instances the parotid glands will be found enlarged also

The percussion sounds elicited will depend upon the amount of involvement of the lungs Emphysema is perhaps the most common finding in the physical examination of the chest Fine rales are sometimes noticeable If the superior mediastinal and peribronchial lymph nodes are greatly enlarged, some dullness to percussion over the sternum and

interscapular area may be elicited. Under these conditions broncho-vesicular breath sounds may be heard.

Roentgen Ray Findings

There are no typical appearances in sarcoidosis that would make roentgen ray studies diagnostically decisive. Widely scattered small soft densities most numerous around the hila and in the bases, is probably the most common finding and the basic condition. However developments incidental to the sarcoid lesions, such as extensive and linear fibrosis, may considerably obscure this appearance. Fibrosed cavities do not rule out a diagnosis of sarcoidosis, but it seems likely, from autopsy reports that such cavities represent an earlier typical tuberculosis.

Lymph node enlargement is usually notable in a roentgen ray study of sarcoidosis and may be so massive as to lead to some mediastinal displacement. Garland found an inexplicable pattern of enlargement of intra thoracic lymph nodes in half his cases—enlargement of both hilar lymph nodes and only the right upper paratracheal nodes.

When the disease is suspected picture of the bones of the extremities should be made. Demineralization of the bones of the hands or feet is quite common and diagnostically very significant.

Laboratory Diagnosis

Positive diagnosis depends upon laboratory identification of tissue specimens at this writing although Warfvinge's experiments with killed acid fast bacilli mentioned in Etiology may lead to injection tests. A tuberculin reaction that is negative or weakly positive is almost invariable and diagnostically helpful.

Blood smears are of no use but chemical studies are useful. The most characteristic findings are hyperglobulinemia and hypercalcemia. A tendency to an inversion of the normal albumin globulin ratio is common. These findings are suggestive; they are not absolute criteria. Other blood abnormalities may be noted if sarcoids interfere with the function of internal organs or glands.

The positive reaction to the injection of a preparation made by maceration of a known sarcoid nodule in saline (Kveim test) is highly suggestive of sarcoidosis. A positive reaction consists of the development of a papule in a period of several weeks. A microscopic section of the papule will show the typical sarcoid nodule. In numerous experiments no case of negative sarcoid involvement gave a positive reaction while in the positive cases nearly all patients reacted positively.



Fig 1 A 23 year old white female complained of dyspnea and weakness for six months Clinical examination revealed no pathognomic findings and laboratory examination was negative The roentgenogram reveals multiple solitary and confluent nodular infiltrations in both lung fields with thickening of both hila and some haziness of the left mid lung field suggestive of secondary inflammation Sputum negative Skin nodule on nose revealed non caseating tubercle Final diagnosis Boeck's Sarcoidosis

Differential Diagnosis

The multiple skin lesions common to sarcoidosis will always be suggestive, and laboratory analysis of tissue specimens will be definitely diagnostic Where such skin lesions do not obtain, however, sarcoidosis of the lung may be mistaken for a form of tuberculosis, metastatic carcinoma, Hodgkin's disease, diffuse, non specific fibrosis, pulmonary congestion or histoplasmosis

Tuberculosis

The roentgenological appearances of sarcoidosis frequently suggests hematogenous pulmonary tuberculosis. I relative good heal Miliary tube the sarcoids are much less uniform in size, non-miliary hematogenous tuberculosis is seldom basal and hilar as sarcoidosis usually is. Repeated negative sputum examinations for acid fast bacilli and biopsy of enlarged lymph nodes may be necessary for final diagnosis.

Metastatic Carcinoma

This condition can likewise be distinguished from sarcoidosis on the basis of presenting symptoms. Further, sarcoidosis is more likely to present enlarged lymph nodes. Its chronicity will confirm diagnosis.

Hodgkin's Disease

Hodgkin's disease will often present enlarged mediastinal lymph nodes, which may also be the out enlargement is, however, much Both diseases may be asymptomat periods of time. The recession of the enlargement of the lymph nodes under roentgen ray treatment indicates Hodgkin's disease but biopsy of affected nodes should be done in all instances.

Diffuse Non-Specific Fibrosis

This condition may be an aftermath of several systemic diseases—measles, whooping cough or scarlet fever—as well as being commonly seen in patients who have chronic bronchopneumonia. The history of such illness is significant. Differentiation must depend upon such a history and upon adenopathy which is characteristic of sarcoidosis but not postpneumonic fibrosis.

Treatment

Favorable results have been observed with the use of adrenocorticotropic hormone (ACTH) and adrenal cortex hormone (cortisone).

References

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Tuberculosis

The roentgenological appearances of sarcoidosis frequently suggests hematogenous pulmonary tuberculosis In most instances the relative good health of the patient will mitigate against such a diagnosis Miliary tuberculosis will be eliminated because the sarcoids are much less uniform in size, non miliary hematogenous tuberculosis is seldom basal and hilar as sarcoidosis usually is Repeated negative sputum examinations for acid fast bacilli and biopsy of enlarged lymph nodes may be necessary for final diagnosis

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INFLUENZA

By ANDREW L BANYAI, M D and J WINTHROP PEABODY M D

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Influenza is caused by a specific virus which has been isolated in two types Smith, Andrews and Laidlaw in England, in 1933, first discovered the type A virus Francis and Magill isolated the type B virus in 1940 It grows in the amniotic sac or on the chorioallantoic membrane of eggs containing growing chick embryo With the aid of electronic microscope, it has been observed in spherical and elongated forms The spherical bodies measures 11 millimicrons

The virus has a marked tropism to the mucus membrane of the air passages and their supportive tissues During the course of the disease, it can never be found in the circulating blood On the other hand it can be recovered from nasopharyngal washings The latter, when sprayed into the nostrils of ferrets mice or hamsters, causes bronchitis pneumonia, or both

Significant findings on postmortem examinations are as follows

1 There is an intense congestion of the bronchial mucosa and submucosa together with edema and thickening

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Influenza is a highly communicable disease of the respiratory tract caused by virus In accordance with accepted standards the usage of this term should be restricted to this clinical entity Its promiscuous application to "common cold," miscellaneous nasopharyngeal infections and pulmonary disease due to Hemophilus influenza (Pfeiffer) is objectionable, for it cannot but lead to confusion in prophylaxis and therapeutics Genuine influenza used to be recognized as the most catastrophic disease of this century It is estimated that it killed twenty-one million people throughout the world during the epidemic of 1918 to 1920 Most likely, the threat of the disease is with us either in unrecognized form or in unknown carriers It is known to occur sporadically during respiratory disease seasons and from time to time, usually several years or decades apart, it assumes epidemic or pandemic proportions Thus, according to available reports, during the winter of 1946 to 1947 from 10 to 15 per cent of the population of Belgium suffered from influenza In various parts of Italy, during the 1948 epidemic, the incidence rate of influenza was from 15 to 30 per cent of the population According to a report of the United States Public Health Service, in 1946 there were 147,749 cases of influenza reported in this country during the first seven weeks of the year

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The virus has a marked tropism to the mucus membrane of the air passages and their supportive tissues During the course of the disease, it can never be found in the circulating blood On the other hand, it can be recovered from nasopharyngal washings The latter, when sprayed into the nostrils of ferrets, mice or hamsters, causes bronchitis pneumonia, or both

Significant findings on postmortem examinations are as follows

1 There is an intense congestion of the bronchial mucosa and submucosa together with edema and thickening

2 The infiltration of the bronchial and bronchiolar walls is dominated by monocytes and lymphocytes, although plasma cells and polymorphonuclear leucocytes are also present

3 The epithelium of the lower air passages may be intact or there is evidence of desquamation even necrosis in the bronchi bronchioles and alveoli In addition the bronchial wall is covered with thick mucoid, purulent or slightly sanguineous exudate and organizing fibrin

4 *A great many of the alveoli are filled with edema fluid which* contains numerous red blood cells, polymorphonuclear leucocytes and fibrin The alveolar walls are thickened with edema, the alveolar capillaries are congested and the lympatics are dilated Hyaline membrane is found on the surface of a large number of alveoli

5 The tenacious exudate may lead to complete bronchial occlusion and thus to small areas of atelectasis

6 *Pulmonary emphysema may be noted in certain segments sub*pleurally or throughout both lungs Its development is brought about by the check valve mechanism of the bronchial exudate which permits the ingress of air to distal portions of the lung but prevents its egress

7 Occasionally, evidence of interstitial emphysema is noted Air which escapes from the alveoli into the supportive tissue of bronchovascular structures passes to the hilar region and enters the mediastinal space *Mediastinal emphysema (pneumomediastinum) which develop* in this manner may be followed by penetration of air into the soft tissues of the neck From here subcutaneous emphysema may spread to the chest or the entire body

8 Rupture of a subpleural emphysematous bullae causes spontaneous pneumonthorax

9 Clear cloudy yellow, seropurulent or serosanguineous pleural *effusion unilaterally or bilaterally is a common complication*

10 Secondary invasion of the lung by other pathogenic microorganisms was quite frequent during earlier epidemics It has been less common in recent years The lung already affected by influenza may represent an organ of lesser resistance in which an overwhelming disease may develop from the settling down of hemolytic streptococcus staphylococcus aureus diplococcus pneumoniae (Fraenkel), Haemophilus influenza, (Pfeiffer) or Klebsiella pneumoniae (Friedlander) The resulting pneumonia may be segmental or lobar in character The associated inflammatory changes increase the likelihood of emphysema and aggravate already existing atelectasis Pneumonia originating from this source

carries serious implications Its possible consequences such as lung abcess bronchiectasis pulmonary fibrosis and empyema are well known Frey noted lung involvement in 17 per cent of 223 cases of epidemic influenza

Usually influenza spreads by droplet infection from one person to another Also there is a possibility of transmission of the disease through the inhalation of contaminated dust Edward (1941) studied this question and ascertained the resistance of the virus to drying When a blanket was impregnated with a suspension of this micro organism it survived drying under ordinary atmospheric conditions and got into the air by shaking the blanket The virulence of the dried virus is maintained virtually unchanged for three days in 10 per cent for a week and in 1 per cent for two weeks Following recovery immunity develops which lasts from six to 12 months At the expiration of this period the way is open for a repeated attack The immunity acquired through infection is type specific Individuals who recovered from type A virus infection remain susceptible to the invasion of type B virus and vice versa Thus apparently the same disease may be contracted within a few weeks There are instances in which neither of these two types of the virus can be identified although the disease runs a clinical course characteristic of influenza Such cases are referred to as influenza Y or influenza X Some clinicians advanced the opinion that these patients did not have influenza at all but some other closely related infection

Symptoms

The incubation period of influenza is approximately two days Experimental observations in volunteers revealed that following nasal instillation of the type A virus influenza developed within 24 to 48 hours With the instillation of type B virus the incubation period varied from 12 to 18 hours There are great variations in the clinical manifestations of influenza As a rule symptoms are milder in sporadically occurring cases than that observed during pandemics Several factors influence the pattern of symptoms, such as the virulence of the micro-organism possible immunity of the individual and the competency of his resistance The latter is dependent upon a number of factors such as nutrition concurrent diseases and others There may be no symptoms at all or but slight indisposition During epidemics at the first outbreak a great many people are affected with a mild form of the disease This is followed by a period during which severe cases are prevalent and the in

cidence of complications is high due to secondary invaders Subsequently, the number of cases decreases without change in the severity of the disease

The onset of influenza is acute or insidious Its symptoms are chilly sensations, or severe shaking chills, fever, lassitude, general fatigue malaise, prostration, restlessness, particularly in children, insomnia anorexia, aching of the back, aching pains in the arms and legs and substernal oppression Flushing of the face, conjunctivitis, coryza are frequently observed Also, epistaxis may occur Hoarseness may be an early complaint The patient is likely to complain of dryness or soreness of the throat The latter may become severe and may be accompanied by dysphagia Cough is a common symptom It is harsh and unproductive at first and may be associated with substernal distress Subsequently, the patient expectorates mucoid sputum which may be grossly bloody Dyspnea develops on the second or third day of illness It is brought about by thickening of the alveolar wall, by dense hyaline deposits on the alveolar surface, patchy atelectasis, emphysema and occasionally, by unilateral or bilateral pleural effusion Development of pathologic pulmonary or pleural changes due to infection with other micro organisms is bound to aggravate the situation Under such circumstances a variety of symptoms and signs are noted which are attributable to bronchopneumonia, lobar pneumonia massive atelectasis lung abscess, empyema and other types of underlying pathologic changes

The duration of influenza is from three to four days in patients who develop no complications

Diagnosis

Due to variations in the severity of influenza, its clinical picture is far from being uniform At its onset it may closely resemble 'common cold The temperature is bound to show a gradual or sudden rise from one day to the other and may reach 104° F (40°C) at the height of the disease The pulse rate is elevated correspondingly but bradycardia may also occur With extensive pulmonary involvement, respirations become rapid labored and there is slight or marked cyanosis The posterior wall of the pharynx, the soft palate and the larynx are congested and there is a moderate swelling of the mucosa in these areas Occasionally, tenderness over the larynx is found and tracheal rales are audible

Physical examination of the lungs may reveal no deviations from

normal Often however, one finds sonorous and sibilant rales widely distributed on both sides Also it is common to detect fine, medium sized or large moist rales over circumscribed symmetrically located areas or throughout both lungs Pleural effusion may obscure the underlying pulmonary disease on one or both sides Complicating atelectasis lobar or bronchopneumonia spontaneous pneumothorax subcutaneous emphysema are diagnosed on the basis of well known findings

Roentgenograms of the chest show irregular mottling extending from both hilar regions toward the periphery Also pleural effusion is readily recognized in this manner Moreover x ray examination is of value in the identification of the aforementioned complications and in closely following the course of the disease

Conclusive evidence of influenza is available in the form of obtaining the virus from the nasopharyngeal washings of the patient Material secured in this fashion is used for intra allantoic inoculation in developing chick embryo The pure culture of the virus obtained in this manner is capable of causing influenza in ferrets mice and hamsters It is well to remember that the throat washings are not positive in all cases of type A or type B of influenza Complement fixation test with specific antigen is diagnostic Beveridge and Burnet (1944) observed positive reaction in adults as well as in children following the intracutaneous injection of a 1 10 dilution of unheated allantoic fluid infected with influenza virus A and B The agglutination inhibition test introduced by Hirst (1940 1942) is of great value in diagnosis He found that antibodies in the serum of patients suffering from influenza inhibited the agglutination of erythrocytes of chicken by the identical virus Usually there is a marked rise of the homologous antibody titer in patients with type A or type B of influenza Exceptions to this rule have been observed not only clinically but also experimentally

Hematologic examinations show leucopenia with decrease in the number of polymorphonuclear leucocytes and with a corresponding increase in the number of lymphocytes There are instances where the leucocyte count remains normal or it is slightly elevated Definite leucocytosis is evident when invasion by secondary pathogens such as pneumococcus streptococcus staphylococcus takes place

Prognosis

Influenza is a self limited disease Mortality rates show great variations according to the virulence of the infecting micro-organism indi

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The treatment of secondary infections is arranged so as to be effective against the causative micro organism Penicillin is given for streptococci, staphylococci and pneumococci Streptomycin aureomycin chloramphenicol or terramycin is administered for Haemophilus influenzae (Pfeiffer) and for Klebsiella pneumoniae (Friedlander) infection

In view of the highly contagious nature of influenza it is mandatory to protect all persons who come in contact with the patient The patient should be instructed to hold a paper napkin over his nose and mouth when he is coughing Immediately after that the napkin is placed in a paper bag and the latter is closed Also a napkin is used for disposing of sputum in the same manner Subsequently the paper bag containing used napkins is burned Persons in attendance of these patients should wear a conventional gauze mask and wash their hands as necessary All eating utensils of the patient are sterilized by boiling

The spread of influenza in dormitories barracks hospitals and elsewhere can be effectively prevented by saturating the air in these places with vapors of propylene glycol in concentrations from 1 2 000 000 to 1 4 000 000 Robertson and his associates in 1941 first demonstrated that influenza virus was killed by such concentrations of propylene glycol Mice exposed to a mist of influenza virus for from five minutes to one hour in a chamber containing propylene glycol remained well All control died Stokes and Henle confirmed this observation Also they found that adequate irradiation of the atmosphere with ultraviolet rays was equally efficacious Both of these methods have been found useful in the prevention of air borne transmission of influenza virus in human beings

It is a well established fact that immunization against influenza is a valuable and practicable method for the protection of people exposed to the virus and for obviating epidemics of influenza As an example of confirmatory evidence in this regard the observations of Francis and his associates may be quoted Following large scale immunization of soldiers the incidence of the disease was 1 15 per cent in the immunized group as compared with an incidence of 9 91 per cent in the nonimmunized group Reports on other recent mass immunizations against influenza closely parallel these figures These findings warrant more extensive use of influenza vaccine in times and places when and where an outbreak of epidemic threatens

Influenza vaccine manufactured by reputable pharmaceutical houses is commercially available in rubber diaphragm capped vial The latter contains a suspension of calcium phosphate adsorbed formalin killed,

vidual and environmental factors which have a bearing on the course of the disease With proper care and treatment, uncomplicated influenza carries a mortality rate less than one per cent even during epidemics It is a matter of common experience that the death rate is greatly increased by supervening secondary pulmonary infections

In some cases, convalescence is characterized by prolonged asthenia, general physical debility and mental sluggishness In such cases, secondary infection may be easily acquired

Treatment

Two principles apply to the management of patients with influenza First, proper care and treatment of the patient Secondly, adequate protection of his personal environment The patient is kept isolated on absolute bed rest He should use bed pan and urinal His diet consists of liquids or semisolid foods The latter should be well cooked Provisions should be made for ample fluid intake in the form of water, carbonated beverages, milk, malted milk, ovaltine, and fruit juices If circumstances require, intravenous administration of 5 per cent dextrose is carried out In this manner, not only dehydration is prevented but also expectoration is facilitated and thus, strenuous cough is alleviated For the relief of the latter, steam inhalations, carbon dioxide oxygen inhalations, codeine sulfate or dicodid is prescribed Restlessness and apprehension may be manifestations of anoxia When this is the case or the patient is cyanotic, oxygen is given by inhalation through a nasal catheter, mask or in a tent For sedation, one should resort to one of the barbiturates Elixir of phenobarbital is given in doses of one or two drachms three times a day Appropriate measures should be instituted for symptoms such as headache, sore throat and constipation For decongestion of the nasal mucosa solutions of neosynephrin in 0 5 to 1 per cent strength in the form of spray or nose drops are useful

Pleural pain should be checked with orally given analgesics (acetylsalicylic acid, acetphenetidine, each in 10 grain (0 3 Gm) doses, three or four times a day), with or without the addition of codeine sulfate or phosphate, one-half of one grain (0 03 Gm) Strapping the chest with adhesive plaster for the relief of pleural pain is an obsolete and objectionable practice It is objectionable because by restricting the respiratory excursions of the chest, it may predispose to atelectasis It is advisable to remove pleural effusion by aspiration repeatedly if necessary, for the sake of relieving dyspnea and of prevention of adhesions

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Influenza vaccine manufactured by reputable pharmaceutical houses is commercially available in rubber-diaphragm capped vials The latter contains a suspension of calcium phosphate adsorbed, formalin killed,

refined concentrated virus produced from the allantoic fluid of
embryo The vaccine is bivalent, it consists of equal parts of type
type B (Lee strain) virus Type A virus is represented by equal am
of the P R 8 and Weiss strains The vaccine should be stored at 3
50° F Under such conditions, it remains stable for about a year
vial should be shaken thoroughly before withdrawal of its content
fluenzal antibodies are often present in the serum of normal indivi
but their level is usually below that necessary for competent prote
Following vaccination, establishment of immunity takes place in a
Hirst and his associates determined the antibody titer of the seru
vaccinated persons They found that it reached its maximum in
weeks after vaccination At this time it was five times that of the
vaccination index It is of paramount importance from the pra
standpoint that they noted that by the end of one year the anti
serum titer was still two and a half times greater than that before v
nation They pointed out that due to this artificial immunity, the a
rate was lower in this group of individuals than in the controls ever
year after vaccination Corroborative observations relative to this
were recorded by Salk and his associates (1945)

Immunization against influenza gives maximum protection v
properly timed in relation to anticipated epidemic outbreaks U
there is inevitable need for it, it is preferable, in general, to vaccina
the fall By the timely use of vaccine absenteeism is substantially
duced in commercial establishments, industrial plants and also,
leaves in the Armed Services.

A new method of immunization was proposed by Freund and
Dermott in 1942 They demonstrated that the immunologic response
prolonged and elevated after vaccination in animals when the vac
was given in the form of a suspension in liquid petrolatum Henle
his associates reported that also in human beings higher immunol
titers could be attained with emulsified vaccines, with slight decreas
the end of six months At the same time, protective levels of serum a
bodies were found only in 60 per cent of the controls who were gi
standard vaccine in isotonic sodium chloride solution On account
occasional local abscess formation, the use of emulsified oil suspens
vaccine has not gained general acceptance

It is well to keep in mind that fai ... lactic v
may result from the difference betwe ... vaccine given
the virus causing the subsequent ep ... of this sort

been recorded by a number of investigators It has been definitely established that the failure of immunization was due to the fact that the epidemic strain of the virus was distinctly different from the standard strain contained in the vaccine, despite both belonging to the same type

From the viewpoint of practical application of vaccination the following items deserve special attention

1 Vaccination is given subcutaneously The dose administered in a single injection, is 1 cc for adults, 0 5 cc for large children and 0 3 cc for small children

2 Local reaction develops occasionally It consists of transient erythema slight induration and tenderness at the site of injection

3 General toxic reactions are common but not serious They are observed in about 50 per cent of the cases with an onset three to four hours after the injection and subsidence in less than 24 rarely 48 hours The symptoms are general aches and pains pharyngitis conjunctivitis, and rarely influenza like manifestations Fever is present in from 1 to 2 per cent It may reach 102° F

4 Influenza vaccine should not be given to persons sensitive to eggs so as to avoid anaphylactic reaction in a hypersensitive individual Prior to vaccination each person should be asked whether or not he is able to eat eggs without trouble Ratner and Untracht suggested the determination of the existence of egg allergy before vaccination by the intracutaneous injection of 0 02 cc of undiluted vaccine

5 Sufficient protection against influenza can be secured by vaccination once a year

6 No sensitization to the proteins contained in the vaccine has been observed

7 Not all vaccinated persons attain high enough antibody titers

8 High antibody titer established by vaccination is not an absolute guarantee of satisfactory immunity

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WHOOPING COUGH
(*Pertussis*)

By ANDREW L. BANYAI, M D and J WINTHROP PEABODY, M D

Whooping cough is an infectious disease acquired by droplet infection from patients suffering from this disease It has world wide distribution and usually, it is encountered in endemic forms According to the statistical bulletin of the Metropolitan Life Insurance Company (1949), there has been a 77 per cent decline in the death rate of whooping cough in children of ages from one to 14 years in the United States between periods of 1931-1935 and 1944-1948

The causative micro-organism of whooping cough, Hemophilus pertussis, is a coccobacillus 0 5 micron in length, which is gram negative and has an ectoplasmic membrane It was first identified by Bordet and Gengou in 1900 and 1906 Whooping cough is most frequent during winter and spring, with the highest incidence in children under five years of age As a rule, it endows the body with a life-long immunity Only very rarely are children or adults seen who acquire it the second time Its incubation period varies from one to three weeks, averaging two weeks

Pathologic findings as noted on postmortem examination of the respiratory tract are

(1) Inflammation of the mucous membrance of the larynx, trachea, bronchi and bronchioles
(2) Formation of tenacious, thick, glary exudate which may occlude the lumen of bronchi and bronchioles
(3) Peribronchitis and peribronchiolitis
(4) Bronchopneumonia
(5) Widespread emphysema
(6) Atelectasis
(7) Bronchiectasis
(8) Interstitial thickening of the alveolar walls
(9) Intraalveolar hemorrhage
(10) Rarely, enlargement of the hilar lymph nodes, pleural effusion and spontaneous pneumothorax

Pulmonary involvement develops early in the course of the disease Pneumonic consolidation occurs in patients with or without fever In the latter group, it is observed in nearly one fourth of the cases Kohn and his associates found pneumonia in 73 per cent of pertussis patients with

low grade fever and in 80 per cent of those with moderate or high fever The pneumonic process is most frequent at the base of the lung Often, it is localized in the perihilar area Affection of the upper lobes is seen in from 10 to 20 per cent *of pneumonic infiltrations In severe cases,* two or more lobes are involved Pneumonic changes may be due to the specific micro organism of whooping cough or to mixed infection Atelectasis is more common in the lower lobes and in the middle lobe than elsewhere Atelectasis is brought about by the occlusion of the *bronchi and bronchioles which is followed by rapid absorption of* the air by the blood stream from areas distal to the bronchial obstruction Atelectasis and pneumonic consolidation may occur in the same lobe Emphysema is present in all typical cases of whooping cough It develops in consequence of partial, check-valve occlusion of the *bronchioles* by *inflammatory* exudate Air inhaled can freely pass the site of partial occlusion during inhalation and thus, it reaches the alveoli But during expiration, the air becomes trapped This circumstance, together with the greatly increased intrapulmonic pressure during strenuous coughing are instrumental in the causation of emphysema Bronchiectasis may *develop during the course of the disease It is* attributable to necrotizing changes in the bronchial wall The damaged bronchi become dilated by the recurrent, tremendously increased intrabronchial pressure during coughing spells

Symptoms

Customarily, the course of whooping cough is divided into three phases

(1) Catarrhal
(2) Paroxysmal
(3) Convalescent

The catarrhal phase *ensues with symptoms* very similar to those of "common cold and lasts from one to three weeks During this period the patient has moderately severe coryza with sneezing and serous rhinorrhea Also, there is slight conjunctival congestion and lacrimation unproductive cough with short, hacking bark, hoarseness and elevation of temperature by 1 to 2° F From this stage of the disease, there is a gradual transition to the paroxysmal stage The latter usually lasts for four weeks, *sometimes longer It is characterized by recurrent* spasmodic coughing spells which vary from a few attacks to 40, sometimes even 60 a day Each coughing episode consists of a rapid succession of short stac

cato coughs in one expiration followed by a sudden deep inspiration and characteristic whoop During the attack epistaxis, hemorrhage from the mouth or pharynx may occur At the end of the paroxysm, the patient may vomit or expectorate tenacious glary sputum and occasionally have involuntary urination or defecation Prior to the paroxysm, the child appears tense and alarmed as if having a premonition of what follows He sits up suddenly and leans forward, trying to support himself during the ensuing coughing spell During the paroxysm, the patient is evidently in acute respiratory distress The eyes are bulging, the neck veins are dilated, there is pronounced congestion in the upper part of the body, together with severe cyanosis

First, there is a constant increase in the severity of each coughing spell, more so during the night Exercise, excitement and sudden undue exposure to cold air are bound to intensify the attacks The characteristic whoop results from a respiratory tussic incoordination A momentary pathologic dissociation of the physiologically coordinated functions of various parts of the respiratory tract develops Consequently, deep inspiration ensues before the tussic closure of the glottis is completely ended There is a functional lag in the contraction of the posterior cricothyroid muscle (abductor of the vocal cords) Because of this deep inspiration takes place while the glottis is still partially closed With reference to the peculiarity of the whoop thus produced, two items are worth remembering

(1) Many infants some children and adults never whoop during pertussis

(2) Some children who had recovered from pertussis may whoop when they contract another severe infection of the lower respiratory tract

Diagnosis

When there is a definite history of contact with a case of pertussis and the typical form of cough is observed, there is no difficulty in establishing the diagnosis During the catarrhal phase, physical findings over the lung are far less than one would anticipate On auscultation, a few *scattered sonorous and sibilant rales and fine moist rales are heard* These changes however, are often absent During the paroxysmal stage of the disease, the patient is afebrile or there is a slight moderate or high elevation of the temperature in the afternoon As an aftermath of the paroxysmal coughing spells, one often notes pronounced subcon

low grade fever and in 80 per cent of those with moderate or high fever The pneumonic process *is most frequent at the base of the lung* Often, it is localized in the perihilar area Affection of the upper lobes is seen in from 10 to 20 per cent of pneumonic infiltrations In severe cases two or more lobes are involved *Pneumonic changes may be due to the specific* micro organism of whooping cough or to mixed infection Atelectasis is more common in the lower lobes and in the middle lobe than elsewhere *Atelectasis is brought about by the occlusion of the* bronchi and bronchioles which is followed by rapid absorption of the air by the blood stream from areas distal to the bronchial obstruction *Atelectasis and pneumonic consolidation may occur in* the same lobe Emphysema is present in all typical cases of whooping cough It develops in consequence of partial, check valve occlusion of the bronchioles by inflammatory exudate. Air inhaled can freely pass the site of partial occlusion during inhalation and thus, it reaches the alveoli But during expiration the air becomes trapped This circumstance together with the greatly increased intrapulmonic pressure during strenuous coughing are instrumental in the causation of emphysema Bronchiectasis may develop during the course of the disease It is attributable to necrotizing changes in the bronchial wall The damaged bronchi become dilated by the recurrent, tremendously increased intrabronchial pressure during coughing spells

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(3) Convalescent

The catarrhal phase ensues with symptoms very similar to those of "common cold and lasts from one to three weeks *During this period* the patient has moderately severe coryza with sneezing and serous rhinorrhea Also, there is slight conjunctival congestion and lacrimation *unproductive cough with short, hacking bark, hoarseness and elevation* of temperature by 1 to 2° F From this stage of the disease, there is a gradual transition to the paroxysmal stage The latter usually lasts for four weeks, sometimes longer It is characterized by recurrent spasmodic coughing spells which vary from a few attacks to 40, sometimes even 60 a day Each coughing episode consists of a rapid succession of short stac

cato coughs in one expiration followed by a sudden deep inspiration and characteristic whoop During the attack, epistaxis, hemorrhage from the mouth or pharynx may occur At the end of the paroxysm, the patient may vomit or expectorate tenacious glary sputum and occasionally have involuntary urination or defecation Prior to the paroxysm, the child appears tense and alarmed as if having a premonition of what follows He sits up suddenly and leans forward, trying to support himself during the ensuing coughing spell During the paroxysm, the patient is evidently in acute respiratory distress The eyes are bulging, the neck veins are dilated, there is pronounced congestion in the upper part of the body, together with severe cyanosis

First, there is a constant increase in the severity of each coughing spell, more so during the night Exercise, excitement and sudden undue exposure to cold air are bound to intensify the attacks The characteristic whoop results from a respiratory tussic incoordination A momentary pathologic dissociation of the physiologically coordinated functions of various parts of the respiratory tract develops Consequently, deep inspiration ensues before the tussic closure of the glottis is completely ended There is a functional lag in the contraction of the posterior cricothyroid muscle (abductor of the vocal cords) Because of this, deep inspiration takes place while the glottis is still partially closed With reference to the peculiarity of the whoop thus produced two items are worth remembering

(1) Many infants some children and adults never whoop during pertussis

(2) Some children who had recovered from pertussis may whoop when they contract another severe infection of the lower respiratory tract

Diagnosis

When there is a definite history of contact with a case of pertussis and the typical form of cough is observed there is no difficulty in establishing the diagnosis During the catarrhal phase physical findings over the lung are far less than one would anticipate On auscultation, a few scattered sonorous and sibilant rales and fine moist rales are heard These changes however, are often absent During the paroxysmal stage of the disease the patient is afebrile or there is a slight, moderate or high elevation of the temperature in the afternoon As an aftermath of the paroxysmal coughing spells one often notes pronounced subcon

junctival hemorrhages Also, there is edema of the eyelids and the face appears puffy Physical examination of the chest reveals a hyperresonant percussion note over both lungs, together with sonorous, sibilant rales and fine moist rales Bronchopneumonic and pneumonic consolidations of the lung are recognized from the impaired or dull percussion note, bronchial or distant breath sounds and from the presence of fine or coarse moist rales over the corresponding area

Roentgenograms of the chest are of great importance for the purpose of ascertaining the patient s pulmonary status The presence of moderate or high fever does not necessarily imply serious pulmonary pathologic changes, although the incidence of pneumonic consolidation is greater in febrile patients than in the ones without fever

The usual roentgenologic findings are

(1) Increased radio translucency of both lung fields indicating the presence of obstructive emphysema

(2) Accentuation of the bronchovascular markings, radiating from the hilum toward the periphery

(3) Scattered small, miliary infiltrations throughout both lungs

(4) Localized, irregular consolidation in the lower lobes which is often confluent with or obscures the cardiophrenic sinus Second in frequency as the site of pneumonic consolidation is the perihilar region The middle and upper lobes are less frequently affected Atelectasis of the lower lobes and the middle lobe appears in the form of a triangular shadow near the cardiac border, with its base on the diaphragm and with its apex pointing toward the hilum Under favorable circumstances atelectatic changes disappear in about two weeks The simultaneous occurrence of pneumonic consolidation and atelectasis in the same lobe is common In severe cases, consolidation may involve the entire extent of one lung Clearing of the pneumonic changes takes from two to three weeks

Bacteriologic confirmation of the diagnosis can be made with the aid of a cough plate containing Bordet Gengou medium or by culturing a specimen obtained with a swab from the nasopharynx Growth of the micro organisms is obtained in from three to four days The time necessary for culture can be reduced to two days by the method of Cruickshank He recommends adding penicillin to the culture medium from half an hour to one hour before planting the culture with the specimen In this fashion, the growth of organisms other than H pertussis is inhibited Still more competent procedure was introduced by Bradford and

his associates They found that when the postnasal pharyngeal swab was moistened with a loopful of penicillin (1,000 units per cc), 92 6 per cent positive cultures were obtained in pertussis cases In comparison when isotonic solution of sodium chloride was substituted for penicillin only 76 5 per cent positive cultures could be secured

Other laboratory examinations are helpful in arriving at a correct diagnosis During the paroxysmal stage and sometimes in the late catarrhal stage, leucocytosis develops with a total white blood cell count of 15,000 or more per cubic millimeter At the same time there is a definite lymphocytosis up to 70 per cent It is well to keep in mind in this connection that such findings are not indispensable prerequisites of the diagnosis Leucocytosis and lymphocytosis are less pronounced in the mixed infection type of pneumonia A normal blood picture does not rule out whooping cough The complement fixation test is positive from 90 to 100 per cent of the cases before whoop develops After the disease reached its height, positive agglutination test and opsonocytophagic index are found Hemophilus pertussis contains three antigenic elements Of these, the agglutinogen fraction can be used for skin testing The intracutaneous injection of purified pertussis agglutinogen is followed by localized edema of 10 millimeters or more in diameter at the site of injection in 24 hours if there is adequate immunity either after the disease or after immunization

In the differential diagnosis of whooping cough the following conditions should be given due consideration

(1) Catarrhal laryngotracheobronchitis
(2) Asthmatic bronchitis
(3) Bronchial asthma
(4) Nonspecific bronchitis
(5) Bronchiectasis
(6) Influenza
(7) Bronchopneumonia and lobar pneumonia of other bacterial rickettsial virus or parasitic origin
(8) Laryngismus stridulus
(9) Aspirated foreign bodies.
(10) Tumors of the trachea and bronchi
(11) Extrinsic compression of the trachea or main bronchi by enlarged lymph nodes aneurysm mediastinal tumors or other mediastinal pathologic changes

Reference has been made to some of the complications which may

occur during the course of whooping cough In addition to these mention should be made of the possible occurrence of encephalitis, bulbar paralysis with consequent inability to nurse, dysarthria, paralysis of the external muscles of the eye and occasionally, optic neuritis Meningeal and cerebral hemorrhages are of grave significance Hemiplegia resulting from such hemorrhages has also been observed Occasionally, repeated attacks of glottis spasm are noted, and rarely, apneic paroxysms Excessive strain during coughing spells may lead to interstitial emphysema of the lung From this, mediastinal emphysema may develop which is often followed by subcutaneous emphysema of the neck and the trunk Also, umbilical and inguinal hernias may make their appearance during cough paroxysms Frenal ulceration of the tongue is a common occurrence in infants and children between one and three years of age It is due to mechanical traumatization during coughing spells

Prognosis

According to available reports the mortality rate of whooping cough was nearly eight per cent in New York City during the period from 1940 to 1946 *The death rate is highest in infants About two-thirds* of all deaths from pertussis occurs in infancy Of all the infectious diseases pertussis, next to influenza, is the leading cause of death The mortality rate is particularly high in patients with pneumonia It is anticipated that the prognosis of this disease will greatly improve with the more uniform use of immune serum and specific antibiotics The usefulness of of these measures cannot be overemphasized

Treatment

There are certain general measures which are essential in the proper management of these patients Isolation and bed rest are mandatory The patient is kept in bed until all clinical manifestations of the disease disappear, including pathologic changes seen on the x ray film The room temperature should be kept at 68 to 70° F Constant nursing attendance is imperative during the paroxysmal stage of the disease During coughing spells the child should be supported in the sitting position with one hand on its forehead Paper napkins are used for collecting the sputum, which after use are put in a paper bag and incinerated

The attending personnel should be trained so that in case of emergency, pharyngeal suction can be carried out, oxygen be administered or a tracheal tube be inserted For suction a No 10 French soft rubber catheter is used for nasal insertion and a No 12 for oral insertion Multi

ple perforations above the unperforated tip of the catheter improve its efficacy

In addition to general hygienic measures close attention must be paid to the patient's nutrition and to the maintenance of normal fluid and electrolyte balance On account of vomiting associated with the paroxysms, frequent small feedings may be necessary Debilitated infants are given liquids with a medicine dropper In some instances prior to feeding these infants it is expedient to remove the accumulated tenacious mucus from the pharynx by suction Rarely, during a few critical days gavage may be necessary When adequate nutrition or fluid intake can not be provided on account of the weakened condition of the patient one should administer parenterally adequate amounts of isotonic solution of sodium chloride, dextrose solution, plasma or whole blood so as to restore and maintain the normal physiologic resistance, defense and repair capacity of the body

The introduction of the systematic use of oxygen for inhalation in the treatment of whooping cough is credited to Kohn and Fischer (1947) On the basis of their clinical experience, they pointed out the advantages of this method Oxygen inhalations not only relieve dyspnea but also alleviate coughing paroxysms and obviate convulsions due to cerebral irritability A transparent, canopy type of oxygen tent is preferable to the administration of oxygen through nasal catheter The atmosphere of the tent contains 50 per cent oxygen and should have a temperature of 68° F and 40 per cent humidity They recommend early placement of infants with anoxia in the oxygen tent rather than to wait until the use of oxygen becomes an emergency measure Experience shows that the inhalation of a mixture of 5 per cent carbon dioxide and 95 per cent oxygen is an excellent means for liquifying the viscous tenacious bronchial exudate Clinical observations reveal that carbon dioxide renders viscid adherent mucus liquid, watery like The liquid inflammatory exudate is expectorated with comparative ease and with relatively little strain In this manner the severity of coughing paroxysms can be greatly relieved Moreover, by liquifying the bronchial exudate with carbon dioxide inhalations development of atelectasis can be prevented and the disappearance of atelectasis already present accelerated Thus one is likely to reduce the incidence of pneumonic consolidation shorten the course of the disease and improve its prognosis The inhalations are given through a nasal catheter to infants and small children and through a face mask to older children and to adults. The adminis

tration of the oxygen carbon dioxide mixture with a flow of 5 liters per minute is scheduled for 10 to 15 minutes three to four times a day, and it is carried on as long as required by the patient s condition

Ether in oil given rectally has been found useful for controlling the frequency and severity of the paroxysms It was first introduced by El good in 1925 into clinical practice For infants one part of ether is mixed with three parts of olive oil All other children are given a mixture of equal parts of ether and olive oil Its dose is one drachm per year of age twice daily for from five to twelve days The ether olive oil mixture is injected into the rectum by gravity through a No 18 or 20 French rubber catheter

Magnesium sulfate is another drug which has been found useful for the alleviation of the paroxysms of whooping cough It is administered intravenously or intramuscularly in the form of a 25 per cent aqueous solution The dose is 0 2 cc per Kg of body weight once daily for 15 to 20 injections

Khalil and Sawfat (1950) observed satisfactory results in the symptomatic treatment of whooping cough with visammin (khellin) It is a b t ter tasting liquid extract of Ammi visnaga and it is sold under various proprietary names It is a vasodilator and it relieves spasm of the bron chial smooth muscles Visammin is administered in syrup in doses of 5 to 7 mg per Kg of body weight per day, divided in three or four doses.

Specific hyperimmune serum is bound to give satisfactory therapeutic results when it is used promptly and in sufficiently large doses The im mune serum is prepared from pooled human blood of adults who had whooping cough in childhood or who had repeated courses of vacci nation with phase I Hemophilus pertussis vaccine the blood being taken one month after the completion of the last course It is available in liquid form or as lyophile serum The latter is prepared by redissolving in sterile distilled water pooled immune serum preserved in powder form after drying in vacuum Its dose is 20 cc given intramuscularly at 48 hour intervals three or four times in succession When the patient s condition is critical from 60 to 100 cc of immune serum are administered in travenously Infants with whooping cough can be effectively treated with 2.5 cc of hyperimmune gamma globulin given intramuscularly daily for four days Often dramatic results are observed from the combined ad ministration of immune globulin and sulfadiazine The latter is pre scribed in doses of 2 grains (130 mg) per Kg of body weight by mouth daily

Streptomycin a product of Actinomyces griseus has been found to have effective bacteriostatic action against Hemophilus pertussis in vitro Favorable therapeutic response has been observed from the administration of streptomycin in experimental murine pertussis Pertinent clinical investigations show striking results from this antibiotic Infants and children are treated with one daily intramuscular injection of this drug Each dose contains 0 3 Gm of streptomycin Children over the age of twelve years adolescents and adults are given a single daily dose of the drug 0 1 Gm per 10 Kg (22 lb) of body weight Treatment is continued until all clinical manifestations of the disease symptomatic, physical and roentgenologic, completely disappear

Considerable reduction in the number and severity of paroxysms as well as in the incidence of complications was achieved by Leichenger and Schultz (1948) with the administration of streptomycin aerosol One gram of streptomycin is dissolved in 8 cc of isotonic solution of sodium chloride and 1 cc of this is inhaled every three hours through an infant sized BLB mask attached to a nebulizer which is connected to an oxygen tank The rate of oxygen flow is 4 to 6 liters per minute The administration of each dose of streptomycin takes from seven to 10 minutes

Prompt therapeutic response can be expected to the administration of terramycin The latter is given orally in doses of 50 mg per kilogram of weight (divided into four doses)

Aureomycin an antibiotic derived from a mold Streptomyces aureofaciens is administered orally in doses of 50 to 100 mg per Kg of body weight per day Individual doses mixed in a cup with a teaspoonful of sweet cherry syrup are given every four hours or every six hours

Chloramphenicol (chloromycetin), an antibiotic derived from cultures of Streptomyces venezuelae and also produced synthetically, is given orally in doses of 60 mg per Kg of body weight for the initial dose (in three divided doses at hourly intervals) and 30 mg per Kg of body weight per day thereafter

Aerosporin another antibiotic, was introduced by Swift in 1948 for the treatment of whooping cough He reported encouraging results from its use Aerosporin is obtained from B aerosporum or B polymyxum the natural habitat of which is the soil For moderately ill patients it is given intramuscularly in doses of 0 4 mg every four hours Severely ill patients are given 0 8 mg aerosporin every three hours

Penicillin should be resorted to as an adjunct when it is definitely es

tablished that complications which developed in the respiratory tract are caused by *micro organisms sensitive to this drug*

In closing, mention should be made of measures for protecting healthy persons from contracting whooping cough There are two successful methods for this purpose, namely, active immunization and passive immunization Active immunization was first introduced by Sauer in 1933 The procedure is as follows Three injections of 1 cc. each of killed alum precipitated Phase I (freshly isolated) H pertussis are administered by deep subcutaneous or intramuscular injection Each cubic centimeter contains 40 billion micro organisms The injections are given four weeks apart, each at a different site, the subcutaneous ones preferably over large muscles Separate needles should be used for withdrawal of the vaccine and for its injection Moderate local reaction is common following the injection Occasionally, moderate fever is noted Infants are immunized between three and nine months of age Following these injections, the development of immunity takes four months Its degree can be accurately ascertained by the complement fixation test or by the agglutination test A stimulating revaccination (activating or booster dose) is given at two years of age and again at school age or at any time between the two after definite exposure to a case of whooping cough The booster dose is 1 cc of the vaccine which contains 40 billion micro organisms It is feasible to give pertussis vaccine in combination with alum precipitated diphtheria and tetanus toxoids, starting at the third month of life Sauer reported that such triple immunization resulted in negative Schick test in 98 per cent of the cases, and in a three plus or four plus pertussis complement fixation test in 92 per cent of all children immunized

Passive immunization is of value in individuals who have been exposed to active cases of whooping cough Active immunization alone would be irrational and useless for immediate protection in such cases on account of the long time necessary for the development of immunity after vaccination Sauer advocates the following schedule for passive immunization Twenty cubic centimeters of human pertussis immune serum are given intramuscularly into the buttocks when the exposure was casual and only for a short time Two 20 cc injections are given at three to five day intervals to those who are non immune and had exposure more than 24 hours The ensuing immunity is immediate, complete and lasts for two weeks Because of the short duration of passive immunity, it is

of advantage to give three injections of H pertussis vaccine subcutaneously in alternate arms within a week

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BRONCHITIS AND BRONCHOPNEUMONIA OF MEASLES

By ANDREW L BANYAI, M D AND J WINTHROP PEABODY M D

Measles (morbilli) is the most common of all communicable exanthematous diseases It is more prevalent in the temperate zone than elsewhere and particularly frequent during spring fall and winter Its incidence has been substantially lower in recent years It is most often seen during early childhood but it occurs at any age The cause of the disease is a filtrable virus which has been isolated on the chorioallantoic membrane of growing chick embryo As a rule lifelong immunity follows recovery from measles, thus repeated attacks are exceptionally rare The disease is transmitted by direct contact through droplet infection the portal of entry being the respiratory tract The incubation period varies from seven to 18 days averaging from nine to 11 days

Ordinarily, measles is thought of as a disease the chief manifestation of which is the skin rash It is often forgotten that involvement of mucous membrane of the upper and lower respiratory tracts is usually present in every case not as a complication but as part and parcel of the disease Denton expressed his conviction which seems to be confirmed by subsequent investigations that the main lesions of measles are in the bronchi and bronchioles, that these lesions are well established by the time the skin rash appears and not infrequently are followed by specific bronchopneumonia Affection of the bronchi and bronchioles was recognized on the roentgenograms of the chest by Kohn and Koransky in 80 per cent of all patients suffering from measles Also they found roentgenologic evidence of bronchopneumonia in 64 per cent of patients less than four years of age and 42 per cent of patients four years of age and over

Postmortem examinations on patients who died from three to 24 hours after the appearance of the skin eruption revealed the following pertinent findings

1 Catarrhal tracheitis, bronchitis and bronchiolitis with intense congestion of the mucosa

2 Early interstitial inflammatory process in the fibrous coats of the lower air passages and its extension into the peribronchial tissues

3 Multiple areas of bronchopneumonia

All these pathologic changes should be considered as specific, mor billigenic as postulated by Koester Clinical observations show that suc pneumonic infiltrations may occur not only during the eruptive phase o the disease, but also either before or after it

Symptoms

Tracheobronchial involvement and bronchopneumonia are accompanied by considerable unproductive, brassy cough and not infrequently by dyspnea, cyanosis, stridor and general toxic manifestations The prodromal symptoms of measles may closely resemble those of a "common cold" and lasts from one to six days During this period there are occasional chilliness, fever from 102° to 104°F. (38 8°—40 0°C), malaise, headache, nervous irritability, marked anorexia, abdominal pain, vomiting, sneezing, coryza and photophobia The temperature drops at the end of the prodromal period only to rise again with the appearance of the skin rash The latter consists of small reddish brown macules which become confluent and form blotchy areas separated from each other by uninvolved skin The exanthem lasts usually for about five days It first develops behind the ears, on the face, forehead and from here, it spreads downward, involving the entire body surface

Diagnosis

Patients with measles present a rather typical appearance One finds edema of the face and eye lids, photophobia, lacrimation and nasal discharge In some cases, enlarged, tender cervical lymph nodes may be noted The presence of Koplik's spots, which were first reported in 1896, is pathognomonic These are pinpoint to pinhead sized whitish papules surrounded by an erythematous aerola Their favorite location is at the posterior part of the buccal mucosa Koplik's spots are usually detectable the day before and for a few days after the development of the skin rash. They may be absent in mild cases and in infants It is well to keep in mind that in certain other conditions, the appearance of the skin may be suggestive of measles These include rubella (German measles), scarlet fever, cerebrospinal meningitis, typhus, typhoid fever, serum sickness, dermatitis due to drugs and dermatitis venenata

On physical examination, signs of bronchitis are usually present over both lungs Over areas of bronchopneumonia fine or medium moist rales are audible and there may be an impairment of the percussion note Physical findings are negative in nearly one-half of the cases with roentgenologically demonstrable bronchopneumonia

Repeated x-ray examination of the chest is of importance from the standpoint of early recognition of pathologic changes in the lower respiratory tract. The following findings may be noted on the roentgenogram

1 Enlargement of the hilar lymph nodes, with or without adjacent homogeneous opacities

2 Disseminated, small nodular shadows throughout both lungs, not unlike those seen in miliary tuberculosis

3 Large homogeneous shadows, representing patchy bronchopneumonic involvement The latter may be localized in various parts of the lung fields, quite frequently in the basal, paracardiac region The gradual resolution and disappearance of the infiltration is a slow process which may take as much as four weeks for its completion

4 Triangular shadows suggestive of atelectasis

Hematologic examination is likely to reveal leucopenia with neutropenia and relative lymphocytosis

Prognosis

Measles is ordinarily a mild disease but severe epidemics do occur from time to time when its course is grave Musser reported that during 1927 1928 in the City of New Orleans the epidemic was so severe that in children of two years of age or under it was almost an exception rather than the rule that they would recover In general, it is a well known fact that the mortality rate is particularly high in infants less than one year of age The fatality rate is over 10 per cent in patients who develop bronchopneumonia In such cases death ensues within the first 10 days of the disease

Treatment

Patients with measles are isolated for at least three weeks They are kept in bed in a well ventilated room with a temperature from 68° to 70° F They should be protected from strong light on account of the photophobia Dark eyeglasses, goggles or eyeshades are of help in this respect The diet should be light and easily digestible Fluid balance should be maintained Sedatives, antipyretics and antipruritic applications are prescribed as required by the patient s condition One half of one per cent solution of neosynephrin can be used for decongestion of the nasal mucosa Boric acid compresses are applied to the eyes In the early stages of bronchopulmonary disease cough is controlled with adequate doses of cough sedatives such as codeine or dicodid When there is considerable accumulation of exudate in the bronchi and bronchioles and its expectoration is difficult in spite of strenuous cough, it is of advantage to give the patient inhalations of a mixture of 5 per cent carbon dioxide and 95 per cent oxygen The gas mixture is supplied in steel cylinders.

A flow-meter attached to the reducing valve of the cylinder is set to 5 liters per minute Inhalations are *given three* to four times a day, each time for a 10 to 15 minute period, and are continued daily until the cough distress is relieved The gas is administered through a face mask or through a nasal catheter

In case it is definitely established that streptococcic, staphylococcic or pneumococcic invasion complicates the clinical picture, the administration of adequate doses of penicillin or other antibiotics is called for Complicating H influenzae infection is treated with streptomycin

Passive immunization has an important role in the prevention of the spread of the disease and also in the reduction of its severity It is the consensus that *complete protection is desirable for all susceptible children* under two years of age Attenuated measles may be attained satis factorily through immunization in children over two years of age *Stiller*man and his associates recommend the following immunization schedule For complete protection the optimum dose after an exposure of from four to seven days 10 cc of concentrated human immune serum for contacts from six to 11 months of age, 15 cc for those from 21 to 23 *months of age, and 20 cc for those from two to three years of age For* modified measles, one should give 5 cc of concentrated human immune serum between the fourth and eighth day after exposure to contacts up to 24 months of age, and 10 cc to those older

Kareletz and his collaborators found that neither aureomycin nor penicillin given to *children with pre-eruptive rubeola, or on the first* day of rash, had any therapeutic effect on the course of the disease, but had an effect on otitis media and pneumonia present on admission and on other complications that developed Gamma globulin given in 225 350 mg doses to 212 measles contacts between the ages of six months and five years, according to a report *made to the Medical* Research Council of London, was followed by development of measles in 31 6 per cent but 94 per cent of these had mo ... of symptoms Adults given 5 ml do ... 5 instances of e ... not prevent development of measles ... per cent sl ... ation

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INVOLVEMENT OF THE LOWER RESPIRATORY TRACT IN SCARLET FEVER

By ANDREW L BANYAI, M D and J WINTHROP PEABODY, M D

Scarlet fever is an acute infectious disease which is endemic in urban areas of the temperate zone According to the statistics of the Metropolitan Life Insurance Company (1949), there has been a 92 per cent decline in the death rate of this disease among children of one to 14 years of age in the United States from 1931-1935 to 1944-1948 Scarlet fever is most frequent during the winter season Its highest morbidity has been noted in children of ages between three and seven years It is rare during the first year of life and over 50 years of age Negroes have a lower incidence of this disease than whites

The diagnosis of scarlet fever is readily made from the history, course, symptoms and physical findings The so-called strawberry tongue is a typical manifestation of the disease The enlarged cervical nodes are tender Evidence of capillary hemorrhages in the skin is common in the form of petechiae The pulse rate is high and out of proportion to the temperature Cultures from the throat and nose are positive for beta-hemolytic streptococci Leucocytosis varies from 10,000 to 40,000 The *Rumpel Leede tests is positive* (appearance of petechiae following application of a tourniquet on the arm for ten minutes so as to produce passive congestion) The Schulz Charlton test *is positive in scarlet fever*, except when the rash is too slight or the rash is too old, with extravasation The test consists of the intracutaneous injection of 2 cc of refined specific *antitoxin at an intensely erythematous area* Consequently, blanching develops at the site of injection in from four to 24 hours

As to differential diagnosis, one should rule out German measles, measles, drug rash and influenza

Involvement of the lower air passages is relatively infrequent It may manifest itself in the form of tracheitis and bronchitis or bronchopneumonia Usually, pulmonary lesions develop as a result of descending infection from the pharynx, but there are instances where specific pathologic changes are simultaneous with the onset of the disease on the pharyngeal mucosa or even precede it Analysis of large groups of patients shows that bronchitis occurs in more than 4 per cent The incidence of bronchopneumonia varies from 0 2 to nearly 2 per cent As a rule, pulmonary changes are detectable during the early course of the disease but bronchopneumonia may develop as late as the third week Pleural effusion may occur in association with a pneumonic infiltration

either as a clear, transparent, serofibrinous exudate or as empyema Bullowa and Wishik reported that 36 per cent of their scarlet fever patients with pneumonia had empyema Rarely, serofibrinous pleural effusion is found without an underlying pneumonic process Also, mention should be made here of the possible, though infrequent, occurrence of hydrothorax in association with glomerulonephritis

Treatment

In the general management of these patients, the following points should be kept in mind

(1) Rest in bed for from eight to 12 days

(2) The patient's room should be well ventilated and kept at a temperature of 68° F (20° C)

(3) Liquid diet while sore throat is present

(4) Insistance on maintaining fluid and electrolyte balance Administration of solutions of dextrose parenterally if necessary

(5) Provisions for adequate vitamin intake

(6) Sedatives if needed

(7) Hydrotherapy for excessive fever

(8) Oral hygiene Gargle with 10 grains (0 65 Gm) of acetylsalicylic acid in half a glass of water

(9) Ice bag to swollen cervical lymph nodes

(10) Mild antipruritic lotions.

Specific therapy can be instituted in two ways

(1) Convalescent scarlet fever serum combined with penicillin

(2) Penicillin without immune serum

Ashley in 1946 recommended as the most satisfactory treatment the intravenous injection of 50 cc or more of convalescent scarlet fever serum within twenty four hours of the appearance of the rash together with the intramuscular injection of penicillin Recent observations show that penicillin alone 300 000 units a day in a single dose or divided doses is fully satisfactory in the treatment of this disease with the exception of very severe cases which require added large doses of convalescent scarlet fever serum Results obtained with the use of penicillin are prompt and dramatic Temperature returns to normal within 24 to 48 hours after the first dose Adequate amounts of penicillin not only cure scarlet fever apparently through the direct effect of this antibiotic upon the causative streptococci but also they prevent complications and obviate the carrier state

Jersild and Munck reported 200 children given procaine penicillin intramuscularly for six days, 120,000 to 300,000 I U once daily and observed over a 6-week period The effect was similar to that obtained from ordinary penicillin given twice daily There were no side effcts

Mathieu and his associates noted that 300,000 units of penicillin given to 386 patients once daily intramuscularly, was as effective as an aqueous solution of penicillin G intramuscularly every 3 hours, 20,000 to 110,000 units, all received treatment for 7 days

Caldwell and his associates found terramycin useful in the treatment of scarlet fever

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DIPHTHERIA OF THE LOWER RESPIRATORY TRACT

By ANDREW L. BANYAI, M D and J WINTHROP PEABODY, M D

According to report of the Metropolitan Life Insurance Company (1949), there has been a 73 per cent decline in the mortality rate of this disease in children from one to 14 years of age in the United States between the period of 1931 1935 and 1944 1948 Commonly, diphtheria is thought of as a disease which involves the tonsils, the posterior pharyngeal wall and the larynx Rarely one encounters instances when the trachea and bronchi are the major or only sites of the pathologic process Tracheobronchial diphtheria is readily recongnizable when it occurs in association with laryngeal involvement The diagnosis of this condition is much more difficult when diphtheria develops in the larger of smaller bronchi without clinical evidence of disease in the upper air passages Also, instances have been observed in which diphtheria followed an ascending course spreading from the bronchi to the larynx The characteristic mucosal lesion consists of a patchy or confluent creamy white exudate which forms a membrane Removal of the membrane from accessible areas leaves a slightly bleeding surface Tracheobronchial diphtheria may be complicated by atelectasis due to occlusion of some of the smaller or larger bronchi Bronchopneumonia is another common complication Emphysema develops in one or both lungs as the result of check valve blockage of the small bronchi In this manner air inhaled has access to the periphery of the lung but has no egress In consequence of ensuing increase in the intraalveolar pressure, air may escape along the bronchovascular structures to the mediastinum The resulting pneumomediastinum (mediastinal emphysema) is likely to spread to the subcutaneous tissues of the neck face and trunk

Diphtheria of the tracheobronchial tract is not the only serious respiratory manifestation of this disease The life of the patient may be threatened in cases of laryngeal diphtheria Also serious respiratory embarrassment may occur during convalescence It manifests itself in paralysis of the posterior cricothyroid muscle which is innervated by the superior laryngeal nerve a branch of the vagus This being the abductor muscle of the vocal cords its paralysis results in spasm of the glottis Moreover paralysis of the respiratory muscles, including the diaphragm is associated with respiratory distress or may cause atelectasis with possible consequent bronchiectasis Purulent bronchitis is another possible complication of diphtheria Analysis of large groups of patients by Bul

lowa and Wishik revealed the occurrence of pneumonia caused by secondary pathogenic micro-organism in 4 1 per cent of the cases

It is beyond the purpose of this chapter to discuss the problem of diphtheria in its entirety Mention should be made, however, of some pertinent salient facts Diphtheria is a communicable, infectious disease caused by the Corynebacterium diphtheriae (Klebs 1883 and Loeffler 1884) The micro-organism is from 1 to 8 microns in length, slightly curved, rod shaped which may have a segmental or granular appearance and it is somewhat thickened at its ends There has been a marked decline in the occurrence of diphtheria during the past decades, with a slight rise in case incidence in recent years It is most common in children between the ages of two to five years Its frequency is higher in winter than during the other seasons It has a gradual or sudden onset following an incubation period of one to 14 days

Symptoms

There are great variations in the symptoms of the disease depending upon its localization and extent, on the virulence of the causative organisms, and on possible complications The constitutional symptoms include chilliness, fever, coryza, malaise, headache, loss of appetite and occasionally diarrhea In pharyngeal diphtheria, the fever is about 102° F, or more, but rarely reaches 104° In tracheobronchial diphtheria, the patient is very toxic and the fever may rise to 105° Laryngeal diphtheria is associated with hoarseness, croupy cough, signs of obstruction of the glottis, such as difficulty in breathing and stridor With tracheobronchial involvement, the cough is intense and croupy in character and it is associated with marked dyspnea, cyanosis and respiratory distress Marked pallor is noted on the patient's face The voice is normal unless diphtheria of the larynx is present If this is the case, the voice is hoarse or there is aphonia

Diagnosis

Tracheobronchial diphtheria greatly interferes with the free access of atmospheric air to the alevoli Consequently, respiration becomes strained, the action of the accessory respiratory muscles comes into prominence There is a marked inspiratory retraction of the suprasternal, supraclavicular and intercostal areas, with or without episgastric and hypochondriac retraction These changes are brought about by the increased intrapleural negative pressure, with its enhanced suction effect The latter is the direct consequence of the lack of pulmonary

expansion which, in turn, is due to widespread bronchial occlusion The percussion note is hyperresonant on account of the extensive emphysema The breath sounds are suppressed In unilateral involvement, these physical findings are detectable on one side only, while on the opposite side the breath sounds are exaggerated There are numerous moist and often sonorous rales throughout both lungs Occasionally, flapping sounds are caused by loose pieces of the inflammatory membrane Complicating massive atelectasis and pneumonic infiltration are recognized by their characteristic physical signs and x ray manifestations The roentgenogram of the chest reveals an emphysematous lung in uncomplicated tracheobronchial diphtheria

Conclusive diagnosis of the disease is reached by the demonstration of Corynebacterium diptheriae in specimens secured by pharyngeal or laryngeal swab or in the bronchial secretion Identification of the microorganism by culture is the conventional diagnostic method

Marked toxicosis is accompanied by leucocytosis up to 10 000 and over, with a simultaneous increase in the immature neutrophile leucocytes

Tracheobronchial diphtheria should be differentiated from conditions liable to cause sudden respiratory distress such as aspirated foreign body, bronchial asthma multiple bronchopneumonias enlarged thymus mediastinal diseases causing compression of the trachea or main bronchi laryngeal edema

In addition to the aforementioned complications diphtheria may be associated with otitis media mastoiditis marked swelling and occasional suppuration of the cervical lymph nodes nephritis, toxic myocarditis endocarditis with the formation of mural thrombi postdiphtheritic paralysis and neuritis Postdiphtheritic paralysis and neuritis may develop in from one to seven weeks after the membranous stage has passed They may involve muscles in various parts of the body Affection of the eye muscles is likely to cause visual disturbances. Involvement of the soft palate and the pharyngeal muscles causes difficulty in swallowing Muscles of the neck trunk and the extremities may become paralyzed Most serious of these manifestations is the possible paralysis of the respiratory muscles, including the diaphragm When this occurs the patient s life is in danger and prompt energetic therapeutic intervention is necessary Otherwise the prognosis of postdiphtheritic muscular paralysis is good Recovery ensues in from four to six weeks.

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In addition to the aforementioned complications, diphtheria may be associated with otitis media, mastoiditis, marked swelling and occasional suppuration of the cervical lymph nodes, nephritis toxic myocarditis, endocarditis with the formation of mural thrombi, postdiphtheritic paralysis and neuritis Postdiphtheritic paralysis and neuritis may develop in from one to seven weeks after the membranous stage has passed They may involve muscles in various parts of the body Affection of the eye muscles is likely to cause visual disturbances Involvement of the soft palate and the pharyngeal muscles causes difficulty in swallowing Muscles of the neck, trunk and the extremities may become paralyzed Most serious of these manifestations is the possible paralysis of the respiratory muscles, including the diaphragm When this occurs, the patient's life is in danger and prompt, energetic therapeutic intervention is necessary Otherwise, the prognosis of postdiphtheritic muscular paralysis is good Recovery ensues in from four to six weeks

Prognosis

The prognosis of tracheobronchial diphtheria is always grave unless the disease is recognized and treated promptly and adequately Similarly, serious prognosis is attached to bronchopneumonia which complicates pharyngeal or laryngeal diphtheria

Treatment

The efficacy of *treatment is directly proportionate* to the closeness of its institution to the onset of the disease *Administration of immune* serum is the specific measure in the management of this condition Intramuscular or intravenous injection of 100 000 units is recommended for effective treatment Prior to the administration of serum, it is imperative to ascertain with the aid of intracutaneous test or the ophthalmic test whether or not the patient is sensitive to serum In case of serum sensitiveness, the patient should be desensitized before the therapeutic administration of serum It is mandatory to have epinephrine and atropin available every time serum injection is given so as to cope with possible severe reactions Penicillin is a useful adjunct in certain instances It obviates or counteracts secondary infective micro-organisms prevents complications caused by pyogens but it does not obviate complications of toxic origin *It is of advantage to give 300 000 units* daily in a single intramuscular injection or the same amount of penicillin in divided doses every three hours for 10 to 12 days Patients with diphtheria of the lower respiratory tract are kept in bed for a period of four to six weeks Adequate nursing care and proper diet are essential When pharyngeal involvement is present liquid diet is ordered Attention should be paid to the maintenance of fluid and electrolyte balance and *sufficient intake of vitamins In some cases* sedatives may be required For this purpose barbiturates should be given rather than morphine In case of difficult deglutition parenteral or tube feeding is indicated Whenever there is danger of laryngeal obstruction and asphyxia due to diphtheritic membrane, attempts should be made at the removal of the latter by direct laryngoscope and *suction When con*servative measures are of no avail immediate intubation or tracheotomy should be done. Respiratory embarrassment resulting from paralysis of the diaphragm is best treated by placing the patient in a respirator

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BRONCHITIS ASSOCIATED WITH MUMPS

By ANDREW L BANYAI, M D and J WINTHROP PEABODY, M D

Mumps is a communicable disease caused by a virus and characterized by a mild fever and swelling of the parotid glands In some instances, the submaxillary and sublingual glands are also involved The disease is most common in children between the ages of five and 15 years Also, it occurs in adults, particularly men of military age Its incubation period is from 16 to 22 days The prodromal period, with malaise, anorexia and headache, lasts from one to three days Subsequently, the patient develops mild fever, soft swelling of one parotid gland which is followed by a similar swelling of the parotid gland on the opposite side in two to three days Localized pain in these areas and painful mastication may be complained of

Its complications include epididymo-orchitis, oophoritis and mastitis (in the female), meningo-encephalitis, presternal edema, pancreatitis and rarely ocular manifestations, such as keratitis, conjunctivitis and iritis

Eagles reports that out of 1,664 soldiers with mumps there were eight cases in which bronchitis could be definitely associated with mumps Even in these patients, the roentgenograms of the lungs revealed no pathologic changes

In addition to symptomatic and supportive measures, aureomycin is given orally in doses of 0 5 Gm every four hours for the average adult Langley and Bryfogle reported striking improvement following the use of this drug Also, chloramphenicol is of value in the treatment of mumps Its daily dosage is 50 mg per Kg of body weight in divided doses

More recent writers have been less sure of the effectiveness of these antibiotics in mumps Shane and Sodero reported a case with no response to aureomycin, Homer and Donovan found no beneficial effects in 24 cases Ghalioungin obtained good results in 4 cases treated with chloromycetin, whereas Nickerson and Worden found that antibiotic ineffective in 57 uncomplicated cases

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PULMONARY INVOLVEMENT IN CHICKENPOX

By ANDREW L BANYAI M D and J WINTHROP PEABODY, M D

Chickenpox (varicella) is a well known, acute, communicable, exanthematous disease of childhood It is very rarely seen in adults It is characterized by the eruption of small, lentil sized vesicles on the skin The vesicles, surrounded by faint erythematous areola are irregularly scattered on the body surface, including the face and the extremities *Occasionally, similar eruptions are observed on the mucous membrane* of the palate, pharynx and larynx Distinguishing feature of this disease is that the exanthem, in contrast to smallpox, does not develop at once over the entire body It appears in small crops over the various parts, with a gradual increase which may take from two to four hours after their appearance and disappear without trace in a few days Due to the serial development of the eruption, one finds on inspection of the skin vesicles in all stages of their course simultaneously

The incubation period is from eight to 17 days, averaging two weeks Usually, there are no prodromal symptoms The appearance of the exanthem is associated with slight elevation of the temperature Rarely the fever may reach 104° F The temperature returns to normal in from one to five days The patients are isolated for a period of one week after the scabs fall off

As stated previously involvement of the mucous membrane of the larynx is infrequent but when it occurs, it is bound to cause marked respiratory difficulties on account of the resulting laryngeal stenosis Even less frequent is the development of pneumonia caused by the virus of this disease Pneumonia attributable to the invasion of secondary pathogenic micro-organisms has been recorded by a number of clinicians Among these, Bullowa and Wishik observed this condition in 0 8 per cent of a large group of patients with chickenpox This incidence is much less than that associated with other communicable diseases of childhood, such as scarlet fever diphtheria, measles and whooping cough On the other hand, empyema as a complication of pneumonia occurs in a greater proportion of cases of chickenpox than of any of the other diseases except scarlet fever

In pneumonia caused by the virus of chickenpox, the local and constitutional symptoms and signs are similar to those seen in bacterial pneumonia Rausch and his associates reported a case of atypical pneumonia complicating severe varicella in an adult Waring and his associates

noted that the histologic findings were characteristic of a virus type of infection of the lung in a fatal case of chickenpox with pneumonia, encephalitis and nephrosis. Grayson and Bradley observed an adult white man in whom chickenpox was complicated by pulmonary disease which showed roentgenologic manifestations of the so-called atypical (virus) pneumonia When first seen, their patient exhibited the usual pleomorphic maculopapular and vesiculopapular rash on the skin, a temperature of 103° F (39 4° C) and persistent cough On subsequent days, the cough became more severe and the dyspnea and cyanosis developed Roentgenograms of the chest revealed only few widely scattered nodular shadows in both lungs at the time of the first examination The findings were more marked on the sixth day after the appearance of the skin rash They consisted of diffuse, finely nodular infiltrations throughout both lung fields, particularly dense in the midportions and about the hilar regions Changes in the perihilar regions were suggestive of pulmonary edema Simultaneously with the progression of pulmonary involvement, numerous moist rales and wheezes were audible over the lungs Fever persisted on the 24th day of illness although clearing of roentgenologic changes was evident on the 17th day The improvement continued and the patient made a complete recovery At the height of the pneumonia leucopenia was found with a relative increase in the lymphocytes No pathogenic bacteria could be recovered from the sputum or from the blood Other pulmonary diseases were ruled out on this basis, with the aid of complement fixation tests and agglutination tests with the serum and by lack of favorable response to sulfadiazine and penicillin Postmortem findings in a case of pneumonia caused by the virus of varicella were recorded by Claudy which we quote "The pleural surface of both lungs showed scattered flat nodular lesions 3 to 8 mm in diameter and were slightly raised above the surrounding surfaces They were reddish white, and the centers were frequently depressed and showed hemorrhage On section, there was extensive consolidation of all lobes of both lungs The consolidation was widely scattered and consisted of numerous small nodules, usually about 5 mm in diameter and frequently coalescent Many of these nodules were hemorrhagic There was much congestion and edema in the lower lobes, but the upper lobes were more uniformly consolidated, with less congestion "

Treatment is symptomatic and supportive Penicillin and aureomycin are useful in controlling secondary infection

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PULMONARY MANIFESTATIONS OF BRUCELLOSIS

By ANDREW L BANYAI, M D AND J WINTHROP PEABODY, M D

Brucellosis is so named after Sir David Bruce who, in 1887 first isolated its causative micro organism from the spleen of a man dead of this disease Because in earlier days a large number of cases have been observed in Malta, the condition has also been designated as Malta Fever and Mediterranean Fever Also, it has been referred to as Undulant Fever, Goat Fever, Bang s Disease, Gibraltar Fever, Rio Grande Fever, and by the French, as Lunatic Fever It is generally recognized that it is a widespread disease, but its prevalence in the United States is not sufficiently appreciated by the medical profession According to Schreiner in 1943 a survey of more than 11,000,000 cattle revealed that 8 per cent of the animals were infected The spread of the disease from infected animals to human beings is a well established fact It is not transmitted from one human being to another It is estimated on the basis of specific skin tests, that approximately 1 per cent of the population of the United States is infected with Brucella which is the cause of this disease In rural areas the incidence is much higher

Three strains of Brucella may infect the human body

(1) Br melitensis (caprine strain) is acquired from the milch goat, which is its chief host and liable to have abortions caused by this micro-organism

(2) Br abortus (bovine strain) isolated by Bang in 1885 which induces abortion in cattle, sheep, mares, rabbits guinea pigs, is less malignant for man than the two other strains

(3) Br suis (porcine strain) cause abortion in swine It may infect cattle and, thus, indirectly, it is transmitted to man Brucella is a short gram negative, non motile coccobacillus All three strains are micro aerophilic Br abortus requires from 8 to 10 per cent carbon dioxide for its growth It may exist outside of the body, for three months in the soil two months in cheese four months in refrigerated butter, and for ten days in refrigerated milk It is destroyed by pasteurization that is, by heating at 145° F (62 7° C) for 30 minutes

Brucellosis is more frequent in men than in women and it is more frequent in adults than in children in spite of the comparatively large amounts of milk consumed by the latter The low incidence of brucellosis in children suggests less susceptibility than that in adults The disease is more prevalent during the summer months Usually, it is contracted by the ingestion of raw milk, cream or unpasteurized dairy

products from cows infected with brucella Direct infection through the unbroken skin may occur in dairy men, milkers, stock handlers, slaughterhouse and packing house workers and veterinarians Occasional infection has been reported in laboratory workers. The incubation period varies from one week to three months Manifestations of the disease may be found in the spleen, liver, gastro intestinal tract, genitourinary tract, heart, blood vessels, central nervous system, lung, eyes, skin, and other organs and tissues Clinical findings may include splenomegaly, generalized enlargement of lymph nodes, involvement of the tonsils, salivary glands, uveal tract, retina, internal eye muscles, endocarditis, phlebothrombosis, bursitis, periarthritis, spondylitis, cholecystitis, colitis, pyelitis, cystitis, oophoritis, orchitis, epididymitis, meningitis and encephalitis

When the lung is affected, the lesion may be localized in the bronchi, the parenchyma or both Various degrees of bronchitis may be noted Rarely, ulceration is found in the trachea and bronchi Increased fragility of the capillaries of the bronchial mucosa may result in hemorrhage Observations of large numbers of proved cases of brucellosis show the occurrence of pulmonary hemorrhage in about 10 per cent Other possible findings are bronchopneumonia, interstitial pneumonitis, pulmonary abscess, pleurisy with the formation of effusion or adhesions Levitt recorded chest findings in 31 per cent of his cases of brucellosis

Symptomatology

With pulmonary involvement, cough is the dominant symptom It may be unproductive or associated with mucoid or mucopurulent expectoration The patient may complain of considerable pain in the chest. The latter originates from the diseased pleura and is accentuated by myalgia and neuritis localized in the thorax None of these symptoms is characteristic of brucellosis but occur in a great many other pleuropulmonary conditions Even so, it is interesting to note that in a group of 228 cases of brucellosis, Haden and Kyger recorded cough as a prominent symptom in 12 7 per cent and observed that respiratory infection was marked in 3 per cent of these cases Other symptoms referable to the respiratory tract include hoarseness, weakness of voice and a peculiar suffocating, smothering sensation which is accompanied by cyanosis and lasts from 15 to 30 minutes

In general, the disease may be acute, subacute or chronic Onset of the acute form is either sudden, with chills and fever which reaches 103°

to 105° F or it may be gradual with a slight elevation of temperature. Intermittent fever with morning remissions is frequent It may last from a few days to weeks The remissions are associated with drenching sweating There may be a musty odor to the perspiration There are instances where the fever shows step like gradations or a sustained high curve In other cases, fever is moderate or absent Other symptoms are chills, flushing of the face in the afternoon, weakness which may amount to prostration, the latter being out of proportion to the fever myalgia, generalized body aches, stiffness, muscle cramps, pain in the neck, headache, arthralgia, sore throat, anorexia, nausea, epigastric and mesogastric and pelvic pains, mental inertia, restlessness, insomnia and possible symptoms of meningitis and encephalitis These symptoms may continue for months, with variable intensity In the chronic form of brucellosis several of these symptoms persist in milder form although exacerbations occur from time to time The recurrence of some of the symptoms at irregular intervals gave the disease its name, undulant fever Presence of pallor and manifestations on the part of the central nervous system are frequent The latter include psychasthenia, mental inaccuracy and despondency

Diagnosis

Pulmonary involvement may be detected on physical and x ray examinations through findings usually associated with bronchitis bronchopneumonia, interstitial pneumonitis, abscess and pleural effusion It is well to keep in mind the limitations of physical findings and the limitations of one s own ability in recognizing pathologic changes by palpation, percussion and the auscultation It has been demonstrated over and over again that negative physical findings do not exclude pulmonary disease

When only bronchial involvement is present, the roentgenogram of the chest may appear normal or it reveals increased bronchovascular markings in both lungs Accentuation of these markings on the x ray film is often more marked at the bases and may be greater on one side than on the other Enlargement of the hilar lymph nodes is frequently seen in these cases Roentgenologic findings encountered in bronchopneumonia interstitial pneumonia and pleurisy are discussed in details in the respective chapters

There are two points of cardinal importance in the diagnosis of brucellosis with pleuropulmonary involvement

1 Examination of the sputum or aspirated fasting gastric contents may reveal brucella by simple staining by culture or by animal inoculation

2 When pleural effusion is thought to be present it should be aspirated and an attempt should be made to recover brucella from it by guinea pig inoculation followed by culture from material obtained from the animal inoculated

Concerning the diagnosis of brucellosis the following items should be given proper evaluation History of ingestion or raw unpasteurized milk or milk products should be considered as suggestive of possible brucellosis However the matter of tracing the infection to its source is not always a simple matter One of our patients an intelligent highly cultured person who was suffering with brucellosis insisted that he consumed nothing but pasteurized milk and milk products Thus for a while we were at a loss as to the manner in which he contracted his disease Then on close questioning he related to us that he was eating customarily a delicatessen raw chopped beef Also it is well to remember that brucellosis may be an occupational disease It is advisable to inquire about previous attacks of unexplained fever and obscure symptoms

On physical examination an ashen gray color of the face may be conspicuous In acute cases an exanthem appears on the skin in about 10 per cent of the cases The skin eruption consists of red irregular small blotches or papules uneven in size and measuring from 2 to 5 mm in diameter The exanthem is roseola like scarlatiniform morbilliform or erythema multiforme exudativum like and it is associated with intense itching which persists from a few hours to four weeks There may be a marked generalized hyperesthesia of the skin not unlike that found in poliomyelitis The pharynx and larynx show moderate or severe congestion The abdomen may be distended and tenderness is noted over areas of visceral involvement The spleen is palpable in about one third of the cases and the liver is enlarged in more than 20 per cent Reference has been made to generalized enlargement of the lymph nodes and involvement of other organs and structures, with concomitant clinical findings In chronic brucellosis the blood pressure is low

Conclusive proof of brucellosis can be secured only by laboratory examinations Of these particular attention should be paid to the following procedures

(1) Culturing the pathogen from the blood

(2) Specific agglutination test with blood serum
(3) Intracutaneous test with specific allergen
(4) Determination of the opsonocytophagic index

1 Culture of brucella is done according to the method of Gould and *Huddleson* The blood culture is rarely positive in chronic cases

2 The agglutination test may be performed in test tubes or on a glass plate The antigen used for this purpose is made of the smooth strain of Br abortus

The rapid agglutination test proposed by Gould and Huddleson (1937) is done on a glass plate which is ruled off into inch squares and is illuminated over a black background The following amounts of the patient s serum are placed in each of these squares 0 08 cc, 0 02 cc, 0 01 cc and 0 005 cc To these, one drop of rapid antigen is added with a standardized dropper so as to make respective serum concentrations of 1 25, 1 50, 1 100, 1 200 and 1 500 The contents of each square are then thoroughly mixed with a clean tooth pick, proceeding from the 1 500 to the 1 25 serum concentration Then the glass plate is removed from the dark field illumination box tilted backward and forward slowly for about two minutes, then replaced on the box, the light is turned on and the results read

Agglutination in a titer of over 1 25 is considered diagnostically significant and means that the patient either has or has had brucellosis Positive agglutination test may be noted on the fifth day of illness, it is more frequent during the second week Foshay pointed out that in some patients with this disease, the agglutination test is positive only during the acute initial phase and seldom or never thereafter In other instances, positive agglutination test is found intermittently at irregular, unpredictable intervals It is evident, therefore, that a negative agglutination test *does not* exclude brucellosis On the other hand, following the first episode of the disease, agglutination capacity of the blood may be retained for many months even for years In chronic cases only low agglutination titer obtains

3 *Intracutaneous test with specific antigen* was first introduced by Burnet in 1922 In recent years, Huddleson s brucellergin has gained wide acceptance It consists of a lipoid free protein nucleate fraction of brucella One tenth cubic centimeter of the *1 2,000 dilution of* brucellergin is injected into the skin on the volar surface of the forearm The reaction is read in 48 hours Erythema alone at the site of injection is without significance A positive reaction *shows in addition to*

erythema, edema or induration which is 0 5 cm or larger Intense reactions may be 7 5 cm or more in diameter One may test simultaneously with intracutaneous injections of the same strength of Br melitensis and abortus in two different sites The reaction is stronger with the antigen which corresponds to the causative micro-organism Positive skin reaction occurs in active disease as well as in patients who had the brucellosis previously, therefore, it cannot be used as a criterion of current brucellosis

4 The estimation of the opsonocytophagic index in brucellosis was recommended by Huddleson and his associates in 1933 According to their observations a positive intracutaneous reaction to brucellergin with negative or low opsonocytophagic index indicates active disease

Examination of the blood reveals mild anemia of the macrocytic hyperchromic type in a large number of cases Calder and his associates attribute these changes to anatomic or functional derangement of the liver, which appears to be a fundamental part of brucellosis as a systemic disease In support of this concept, they point out that low grade jaundice as measured by the van den Bergh reaction is not uncommon and that this reaction is the delayed type, which ordinarily is associated with structural damage of the liver parenchyma Leucopenia with relative lymphocytosis is frequent in acute cases and it is found in about one third of the chronic cases Calder and his associates observed that 76 per cent of their patients with brucellosis had more than 30 per cent lymphocytes and 16 6 per cent had more than 50 per cent lymphocytes Another important finding was active lymphocytogenesis characterized by the appearance of immature lymphocytes in the peripheral blood, a so called shift to the left in the hemogram of these blood cells Also, these authors reported that the coagulation of the blood was slow, often incomplete and that the clot retraction was imperfect There are instances with eosinophilia in the peripheral blood This, together with x ray evidence of bronchopneumonia or interstitial pneumonitis, may bring to mind Loeffler's syndrome

Differential Diagnosis

It is beyond the scope of this chapter to deal with the differential diagnostic aspects of brucellosis in general Relative to the pulmonary forms of this disease, particular attention should be paid to ruling out tuberculosis, influenza, bronchitis, pneumonia and abscess caused by other pathogens Moreover, diseases which may simulate these condi

(2) Specific agglutination test with blood serum
(3) Intracutaneous test with specific allergen
(4) Determination of the opsonocytophagic index

1 Culture of brucella is done according to the method of Gould and Huddleson *The blood culture is rarely positive in chronic cases*

2 The agglutination test may be performed in test tubes or on a glass plate The antigen used for this purpose is made of the smooth strain of Br abortus

The rapid agglutination test proposed by Gould and Huddleson (1937) *is done on a glass plate which is ruled off into inch squares and* is illuminated over a black background The following amounts of the patient s serum are placed in each of these squares 0 08 cc, 0 02 cc 0 01 cc and 0 005 cc To these, one drop of rapid antigen is added with a standardized dropper so as to make respective serum concentrations *of 1 25, 1 50, 1 100, 1 200 and 1 500* The contents of each square are then thoroughly mixed with a clean tooth pick, proceeding from the 1 500 to the 1 25 serum concentration Then the glass plate is removed from the dark field illumination box, tilted backward and forward slowly for about two minutes, then replaced on the box, the light *is turned on and the results read*

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tions should be excluded For pertinent details the reader is referred to the respective chapters

Prognosis

Untreated and inadequately treated cases of brucellosis have a tendency to chronicity and recurrences Interestingly relapse has been often observed in patients with mild symptoms at the onset of the disease Brucellosis does not predispose to tuberculosis

Prior to present day methods of treatment death from brucellosis was reported in from 2 to 5 per cent of the cases The fatal outcome was due to localization of the disease in the brain heart or lung Death from pulmonary embolism was recorded by Roger and Audier and others

Treatment

Before discussing this problem attention is called again to the known prevalence of this disease in the United States This calls for an urgent campaign for the education of the public as well as for improved State and Federal laws with special reference to the consumption marketing and distribution of dairy products and other items which may spread the disease

Patients with pulmonary manifestations of brucellosis are treated by general supportive measures by methods directed toward the relief of symptoms originating from the lung and by specific therapy The first two of these should follow general principles which apply to the management of systemic infectious diseases Special thought should be given to the correction of anemia Some clinicians expressed the opinion that thiamine hydrochloride and niacin are capable of enhancing the opsonic activity of the patient s blood

Spink and his associates observed satisfactory results in patients treated simultaneously with sulfadiazine and streptomycin On the basis of their experience they recommend the following schedule Sulfadiazine is administered orally with an initial dose of 4 Gm and then 1 Gm every four hours for two to three weeks Streptomycin is administered intramuscularly in 0 5 Gm doses every six hours for seven days for a total of 14 Gm Also Pulaski and Amspacher (1947) reported favorably on the combined use of sulfadiazine and streptomycin in brucellosis Eisele and McCullough noted striking results in a case of severe brucellosis following the simultaneous administration of these two drugs The clinical response consisted of a prompt and abrupt cessation of the fever

disappearance of a prolonged septicemia and a seventeen month clinical well-being without relapse. They administered daily 12 Gm. of sulfadiazine and 6 Gm. of streptomycin

Uniformly good results were obtained by Spink and his associates with the use of aureomycin in the treatment of acute and chronic brucellosis caused by Br melitensis

Aureomycin is an antibiotic derived from the mold Streptomyces aureofaciens The recommended doses of the proprietary preparation of this drug, "duomycin" (Lederle), 0 1 Gm in four divided doses given orally the first day, 0 6 Gm the second day, 1 6 Gm the third day and from then on, a total daily dose of 4 to 6 Gm for two weeks With this schedule, the only side effects were transitory nausea, vomiting, and diarrhea which, however, do not interfere with the continuance of the treatment

Another treatment schedule which has been found useful, calls for 50 mg of aureomycin per Kg of body weight per day for 10 days Herrell observed the best therapeutic results from the oral administration of 3 Gm aureomycin per day, with the simultaneous administration of 2 Gm of dihydrostreptomycin intramuscularly per day

Chloramphenicol (chloromycetin), another antibiotic, is effective in the treatment of brucellosis The initial dose, given orally, is 50 mg per Kg of body weight On successive days, the maintenance dose is 0 25 Gm of the drug, given in capsules, every three hours for at least seven days after the patient is afebrile

Terramycin therapy has been effectively used by some practitioners A dosage of 100 to 150 mg per kg daily for 28 days, brought definite response without relapse, as noted by Tyson and Hobby, whereas similar doses given for 5 to 7 days only were followed invariably by relapse

Terramycin is said to be better tolerated than aureomycin Some report a tendency to relapse after aureomycin therapy

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PULMONARY DISEASE ASSOCIATED WITH ERYTHEMA MULTIFORME EXUDATIVUM (HEBRA)

By ANDREW L. BANYAI, M.D. AND J. WINTHROP PEABODY, M.D.

(Synonyms: Mucosal respiratory syndrome, Stevens-Johnson disease.)

Erythema multiforme exudativum (Hebra), designated as erytheme polymorphe in France, is an airborne, systemic, infectious disease, most likely of viral origin, first defined by Hebra in 1860. Its most characteristic manifestation is a cutaneous eruption which appears in two forms:

(1) Erythemato-papular
(2) Vesiculo bullous type

The condition is known to occur endemically, particularly in members of the same family, and in groups of military personnel living in the same quarters. Its highest incidence is observed in both sexes of young adults but children and the aged are not exempt. It is more frequent in the autumn and spring. The skin lesion begins on the dorsal surface of the hands and feet and from here spreads to the extensor surface of the upper and lower extremities and to the side of the neck and face. The trunk is rarely involved. In about 25 per cent of the cases, the skin lesion is associated with involvement of the mucous membrance of the lips, nose, mouth, pharynx and laryngotracheobronchial structures. Also, the conjunctiva, urethral meatus, glans penis, vulva and vagina may be affected. The latter type of erythema multiforme was first recognized as a clinical entity by the French dermatologist, Rendu, in 1916. He designated it as ectodermosis erosiva pluriorificialis. Some times it is also referred to as Klauder's syndrome, after the Pennsylvania physician who dealt with this subject in great detail in 1937. In some instances, pathologic changes in the mucous membrane precede the skin lesion by one to two weeks.

Typical involvement of the skin and mucous membrane begins as an erythematous macule. This is followed by the formation of vesicles or bullae which, in turn, become desquamated and change into superficial ulcers. Sometimes, only few ulcers are noted on the mucosa. In other cases, the ulcers become confluent and occupy large areas. The ulcerated mucosal areas are covered with a thin, grayish white pseudomembrane. The lesions have a tendency to recurrence. Enanthematous manifestations are more common in the vesiculo-bullous variety of the disease.

Postmortem findings in the lung of patients who died of this disease

have been recorded by several investigators We quote Stanyon and Warren "The gross appearance of both lungs was similar They were heavy, firm and meaty throughout The cut surface failed to retract and the margins were sharp The changes were fairly uniform throughout, the parenchyma assuming a peculiar reddish gray, solid appearance which was associated with a certain translucency making the delicate interlobar septa stand out fairly prominently On pressure, an excessive quantity of slightly frothy fluid oozed from the cut surfaces while thick, creamy material could be squeezed from the smaller bronchi The peribronchial and mediastinal lymph nodes were markedly enlarged " Finland and his associates reported on the necropsy findings in three fatal cases Microscopic examination of typical areas of patchy miliary infiltration showed

"(1) Interstitial infiltration with various kinds of mononuclear cells, predominantly plasma cells,

"(2) Swelling of the alveolar lining cells with occasional mitoses and

"(3) An alveolar exudate consisting usually of large mononuclear cells and desquamated alveolar lining cells, but in some areas containing only precipitated albumin and red blood cells "

Additional findings include a generalized moderate enlargement of the lymph nodes and occasionally, moderate splenomegaly When the enlargement of the lymph nodes is localized in the neck, the condition may simulate infectious mononucleosis In some instances, edematous swelling of the hands and feet, in others periarticular edema have been observed

The cause of this disease is not known, but it is assumed to be of viral origin Finland and his associates found evidence suggestive of a psittacosis virus like agent in three out of four of their cases

The symptoms of this syndrome are predicated upon the severity of infection and the extent of pulmonary involvement Patients with the vesiculo bullous form of the disease are likely to have constitutional symptoms, such as chilliness, fever and malaise Fever may be slight but may reach as high as 105° F (40 5° C) Premonitory symptoms are similar to those seen in the so called common cold or upper respiratory infection These include coryza, sore throat, hoarseness, slight, moderate or severe cough, headache and swelling of the cervical lymph nodes Cough is unproductive at the onset Subsequently, it changes into one with moderate expectoration of tenacious, mucopurulent spu

tum Also, the patient may complain of itching of the eyes, photophobia, sore mouth, profuse salivation, drooling of purulent material from the mouth and occasionally of difficulty in swallowing and substernal pain

Fever persists from two to several weeks during which the patient shows other signs of toxicity The elevated temperature runs an irregular remittent or intermittent course In addition to cutaneous changes, mucosal involvement becomes noticeable from a few days to the tenth day of illness The lips are swollen and may be cyanotic and showing few vesicles The oral and pharyngeal mucosa is congested, numerous small and moderate sized blebs appear, which soon rupture and the mucosal surface becomes coated with a thin exudate The submaxillary lymph nodes are enlarged and tender In a substantial percentage of patients with marked involvement of the respiratory tract, cutaneous eruption is absent

Physical examination of the chest reveals the presence of diffuse sonorous and sibilant and fine or medium sized moist rales over the involved areas Physical findings over the chest may be negative for days while x ray manifestations become noticeable The latter appear in the form of exaggerated bronchovascular markings, feathery pneumonic infiltration localized in the middle lobe or in one or both lower lobes Often, the lesion appears to be radiating from the hilar region and may closely resemble the x-ray appearance of atypical (virus) pneumonia

Other clinical findings include congestion of the laryngeal structures The latter show ulceration and mucosal exfoliation in severe cases A moderate, generalized adenopathy and occasionally, splenomegaly and an apical heart murmur may be found

Laboratory findings are not diagnostic Leucocytosis is present during the febrile period It may reach 20,000 per cubic millimeter Sometimes leucopenia is found The differential count of the white blood cells remains normal in most instances, although one may find an increase in the number of polymorphonuclear cells up to 87 per cent and of the eosinophiles up to 8 per cent In some patients, diagnostically significant cold hemagglutinin titers are found in the serum

As to the prognosis general and localizing manifestations of the disease usually begin to improve in from two to three weeks The total duration of the disease is from five to six weeks The outlook for recovery, however is far from being always favorable. As a matter of fact,

in patients hospitalized with this condition, there is a mortality rate of 11 per cent

The treatment is general supportive and symptomatic. The oro pharyngeal lesion may be treated by the local application of hydrogen peroxide or *sodium perborate mouth wash* or by gentian violet medicinal Appropriate measures are carried out for the conjunctival in volvement In some cases with severe involvement of the mouth and throat, ordinary food intake is impossible, and the parenteral adminis tration of fluids, dextrose, electrolytes and amino acids becomes neces sary

Ayers recommends sulfadiazine and sodium bicarbonate 1 Gm each every four hours or intragluteal injections of penicillin (300,000 units daily for several days) Also, chloramphenicol, aureomycin or terramycin therapy may be tried Robinson used aureomycin orally successfully in three cases Wammock and his collaborators noted rapid and dramatic improvement in a patient treated with pituitary adrenotropic hormone The patient was given 25 mg of this drug every eight hours for a total of six doses, followed by 25 mg once daily for three days

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SYPHILIS OF THE LUNG

By ANDREW L BANYAI, M D AND J WINTHROP PEABODY, M D

The subject of pulmonary syphilis is usually approached with a great deal of hesitation This is most likely due to the apparent infrequency of this condition The skepticism of Lord is still shared by a great many clinicians He said "The diagnosis of pulmonary syphilis cannot be made with assurance during life, and is often uncertain at the postmortem examination" Difficulties arising from the latter have been recognized by a number of pathologists who pointed out the close resemblance of gumma and tubercle on macroscopic as well as on microscopic examination Also, it is known that spirochetes are rarely found in the diseased area On the other hand, Moissejew described double refracting lipoid bodies in such lesions Tanaka observed the presence of smooth muscles in syphilitic scars of the lung As an illustration necropsy findings recorded by Freedman and Higley in a case of syphilitic gumma of the lung is of interest It was an egg shaped mass measuring 7x3 5x3 5 *cm*, sharply demarcated, with a homogeneous, gray granular cut surface The histologic examination revealed "large areas of homogeneous necrosis surrounded by zones of vascular granulation tissue There were fibroblasts and mature fibrocytes The cellular content of the granulation tissue was chiefly lymphocytic There were occasional plasma cells and endothelial cells The newly formed capillaries were thin-walled and here and there were small foci of perivascular lymphocytic infiltration In some sections the necrotic *zones were seen* infiltrating and destroying the walls of small bronchi and vessels In one section, the necrotic area was adjacent to a large bronchus, the wall of *which* showed a marked diffuse lymphocytic and plasma cell infiltration with ulceration of the lining mucous membrane *The adjacent* pulmonary parenchyma showed extensive edema, hyperemia, with leucocytic and mononuclear exudates in *the alveoli Here and there were* small foci of purulent necrosis"

The incidence of pulmonary syphilis on routine *postmortem* examination, as reported by several authors, in this country and abroad, varies from 0 03 to 3 4 per cent

For *the complete* elucidation of this problem, investigations *should* be mentioned which deal with the occurrence of syphilis *of the* lung in persons with known syphilis Postmortem examination *of these* individuals showed the presence of pulmonary syphilis in from 2 to 12 per cent of the cases[f]

The vagaries of syphilis are reflected in a number of interesting points graphically presented by Morgan

(1) Syphilitic infection is asymptomatic in from 33 to 35 per cent of the cases and spontaneous 'cure occurs in from 25 to 35 per cent Syphilitic infection is followed by cardiovascular involvement in 10 to 15 per cent by neurosyphilis in about 10 per cent by benign tertiary syphilis in 10 to 15 per cent According to Howard (1924) the incidence of pulmonary syphilis to syphilis of other organs is 1 20 Males are affected twice as often as females The onset of clinical manifestations takes place from five to 10 years after the primary infection but the appearance of pulmonary involvement may be as late as thirty years Rarely syphilitic pneumonia develops early from involvement of the upper respiratory tract As to localization the right lung is more often involved than the left The disease is bilateral in from 20 to 50 per cent of the cases Usually the middle and lower lobes are affected but all lobes may be involved simultaneously or one of the upper lobes alone

Various forms of pulmonary syphilis are recognized

1 Gummas
2 Chronic interstitial pneumonitis
3 Bronchopneumonia and lobar pneumonia
4 Sclerosis of the pulmonary vessels
5 Mixed forms

(1) The gumma varies from miliary syphilomas to orange-sized or larger lesions The involvement frequently begins at a site near the hilum and extends toward the periphery Rarely nodular alveolar changes are found on postmortem examination Usually one notes concomitant alterations in the tissues adjacent to a gumma These include congestion edema interstitial hemorrhage fibrosis atelectasis and emphysema Cavitation may occur but it is far less frequent than tuberculosis Calcification is a very rare sequel

(2) Chronic interstitial pneumonitis is bound to result in fibrosis which spreads fan wise from the hilum along the bronchovascular structures Fibrotic changes often invade the pleura The latter becomes thickened and shows firm band like adhesions Thickening of the interlobar pleura is likely to be present Extensive pleural fibrosis has a tendency to lead to marked contraction of the affected hemithorax

(3) Bronchopneumonia and lobar pneumonia are characterized by monocytic infiltration The gross lesion consist of nodular or diffuse multiple gummas Massive fibrosis (carnification) is likely to result from it.

with consequent obliteration of the alveoli Intense fibrosis may be followed by localized necrosis Clinically, extensive fibrosis is associated with marked decrease in the hemithorax involved, displacement of the mediastinal structures (trachea, large vessels, heart) toward the site of fibrosis and an upward shift of the corresponding hemidiaphragm Pulmo lobatus is one of the manifestations of pulmonary syphilis It is characterized by massive cirrhosis of the lung, with deep retractions of its surface Congenital syphilis of the lung is encountered in two forms

(a) Small, cherry stone sized multiple gummas

(b) Penumonia alba The latter shows alveolar as well as interstitial infiltration If the newborn infant survives with pneumonia alba, the symptoms are, as a rule, less marked than in a case of pneumonia of acquired bacterial origin of the same extent

4) Detailed discussion of sclerosis of the pulmonary vessels is presented in the chapter on Sclerosis of the Pulmonary Artery

As a rule, vascular walls are affected in all of their layers The consequent necrosis of these structures may lead to the formation of aneurysm Favre and his associates (1937) called attention to a peculiar form of pulmonary syphilis which is characterized by autochtonous infarcts of arterial origin On necropsy, the vascular lesion is found to be disseminated in the entire lung within the parenchyma which shows more recent signs of specific involvement There is evidence of multiple vascular thromboses of different ages, associated with necrosis and hemorrhage Also, localized pulmonary artery thrombosis may occur in association with syphilitic pneumonia

There are a number of complications limited to the chest which are likely to aggravate the clinical course of the disease These include gummatous bronchitis, obliterative bronchiolitis, bronchiectasis, lung abscess atelectasis, emphysema, pleural thickening, pleural effusion, empyema and cor pulmonale Involvement of the bronchi varies from superficial mucosal changes to severe destruction of these structures The former occurs during the secondary phase of syphilis as we have observed in some of our cases In addition to congestion and edema of the bronchial mucosa, syphilitic changes may appear in the form of erosion by smaller or larger superficial or deep ulcers The latter may completely destroy the bronchial wall, including the cartilage of larger bronchi Fibrinous deposits may cover the surface of these ulcers Perforation into the surrounding parenchyma and blood vessels occurs Fibrosis which results from gummatous a dense, tough scar tissue which is

likely to extend along the bronchial branches to their finest ramifications Peribronchial fibrosis may be predominantly longitudinal, which runs parallel to the axis of the bronchial tubes, or it is spiral or circular Circular fibrosis, at times, completely encases certain areas and constricts, or obliterates the bronchial lumen Syphilitic affection of the bronchi may bring about the development of bronchiectasis in three ways First, gummatous infiltration weakens the wall so that it dilates and becomes deformed under the effect of the stress and strain of the greatly increased intrapulmonic pressure during coughing spells Secondly, fibrostenosis of considerable degree is bound to obstruct the adequate evacuation of mucus from the corresponding bronchial tract lying distal to it While in this manner the natural defense mechanism of the implicated bronchus is interfered with, the distally located bronchi become predilectional sites for the settling down of pathogenic micro organisms These, in turn induce nonspecific inflammatory changes which may end in bronchiectasis Thirdly, interstitial pulmonary fibrosis, which develops in the wake of syphilitic infiltration, has a marked tendency to contraction The contracting scars may exert traction upon the wall of adjacent bronchi and thus, cause bronchiectasis

The number of reported cases of syphilitic pleurisy is rather small According to Orszagh, the plastic or exudative form may be found in the secondary stage or in the third stage, with or without involvement of the underlying parenchyma He suggested that obstinate, often recurring cases of pleurisy with effusion, which last for years, should be suspected of being syphilitic in origin A serologic test which is more positive for syphilis in the pleural exudate than in the blood serum is thought to be suggestive of syphilitic pleurisy Therapeutic tests may prove to be of great value in problematic cases of long standing The onset of syphilitic pleural effusion may be acute One of our patients, a 31 year old white man, complained of sudden chills, fever, moderate cough and pain in the right side of the chest of three weeks' duration Physical and x ray examinations revealed a large pleural effusion on the left side, with displacement of the heart to the opposite direction Thorough search for tubercle bacilli in his sputum gave negative results Wassermann test of the blood was four plus During a five week period, large amounts of pleural fluid were removed by aspiration on repeated occasions The effusion was serosanguineous It contained a high percentage of lymphocytes. Guinea pig inoculation with the pleural fluid was negative for tuberculosis The patient died unexpectedly Postmortem examination

revealed histologically confirmed scattered large gummas in the left lung and pleura

Symptomatology

Pulmonary changes due to syphilis may develop without symptoms In other instances, following an insidious onset the well known symptoms of chronic *pulmonary affections are experienced by the patient* There is more or less cough which occasionally appears in paroxysms on exertion or is associated with whooping The latter is explainable on the basis of cicatrical bronchial *stricture or granulomatous penetration of* a mural gumma into the bronchial lumen Expectoration may be entirely absent or the amount of sputum varies from slight to eight ounces in 24 hours When bronchiectasis or abscess is present the sputum may have foul odor Pulmonary hemorrhage is frequent, varying in amounts from blood streaked sputum to a pint of blood Fatal pulmonary hemorrhage has also been observed Chest pain originates from two possible sources

(1) From involvement of the pleura

(2) From cardiovascular disease

The latter is the cause of pain either as part of aortitis or angina pectoris syndrome or because of pressure of an aortic aneurysm Pain caused by *aortic aneurysm is attributable to pressure upon the sternum* and it is of a constant, dull aching or boring character Also, pain may occur in other parts of the chest when the pressure of an aneurysm is exerted upon other sensitive thoracic structures Depending upon the extent of gummatous involvement and fibrosis dyspnea will be noted Usually, it has a slowly increasing tendency *It is well to bear in mind that in* case there is a co existent aortitis or aortic regurgitation with failure of left side of the heart, cardiac asthma and dyspnea of cardiac origin aggravate the patient s condition Slight elevation of the temperature and night sweats are not infrequent High fever is rather rare It occurs in acute syphilitic pneumonia, *such as reported by Ornstein and by* Hartung and Freedman, and is preceded by chills The general nutritional condition is, as a rule very little affected There are exceptional instances [illegible] ded One should

[illegible]

manifestations on the part of the central nervous sy[illegible] ent, severe headache particularly at night, visual disturbances lancinating pain ataxia unmotivated euphoria, *mental deterioration and urinary*

Diagnosis

Clinical diagnosis of pulmonary syphilis is impossible without discriminating attention to all available information and findings Lack of a history of syphilitic infection with primary and secondary manifestations does not rule out syphilis As stated by Morgan asymptomatic infection occurred in from 33 to 35 per cent of the cases There may be a history of miscarriages or repeated attacks of influenza or pneumonia

Physical findings depend upon the site extent and type of the pulmonary lesion There is nothing characteristic about them Percussion and auscultation reveal changes encountered in acute subacute or chronic forms of various affections of the lung those of pleural thickening or pleurisy with effusion There may be limitation in motion and contraction of one side of the chest when extensive unilateral fibrosis dominates the picture Long standing massive unilateral involvement is bound to lead to signs of compensatory emphysema on the opposite side In any event it is well to keep in mind the possibility of pulmonary syphilis in chronic lesions localized in the lower one half of one lung which have no other obvious explanation In general a striking discrepancy between signs and symptoms the latter being few and insignificant as compared with the former should prompt one to consider pulmonary syphilis as a possibility Also extrapulmonary stigmas of syphilis should arouse suspicion of possible involvement of the lung In this regard one should think of the proper diagnostic interpretation of generalized enlargement of the superficial lymph nodes co-existent laryngitis bone lesions such as late periostitis osteitis osteomyelitis and Charcot joint signs of congenital syphilis such as interstitial keratitis saddle nose perforated nasal septum eighth nerve deafness Hutchinsonian teeth and saber tibiae Also thorough search should be made for signs of syphilis of the central nervous system In case of diastolic and systolic murmur at the second intercostal space right to the sternal border syphilitic valvular involvement should be thought of with aortic regurgitation Large syphilitic aneurysm of the aorta may cause bulging of the anterior chest wall Also aneurysm of the aorta should be suspected from the Oliver Cardarelli sign tugging on the larynx pushed upward with the fingers. Aneurysm of the pulmonary artery can be tentatively diagnosed from the presence of systolic pulsation and thrill in the second interspace to the left of the sternum

Among incidental findings mention should be made of clubbing of the fingers that may be noted in pulmonary syphilis This finding is far

from being pathognomonic of this disease It is well to bear in mind that it may occur in a good many diversified conditions These include tuberculosis, lung abscess, bronchiectasis, chronic bronchitis, extensive pulmonary fibrosis from any cause, bronchial asthma, emphysema, primary and metastatic malignant tumors and arteriovenous fistula of the lung, essential pulmonary hemosiderosis, empyema, neoplasms of the pleura and mediastinum, congenital heart disease, subacute bacterial endocarditis amyloidosis, infestation of the lung with entameba histolytica and other animal parasites, chronic kidney disease, chronic liver disease, ulcerative colitis, intestinal polyposis and also, clubbing of the fingers may be familial

X ray shadows cast by lung changes caused by pulmonary syphilis show a variety of appearances The involvement may be lobar in extent or patchy, however, regardless of its extent, it is more common in the lower one half of the lung than elsewhere In some instances, solitary or multiple, small, medium or large sized round or oval shadows with sharp outlines are seen These may be associated with adjacent segmental or lobar atelectasis which develops from compression of the corresponding bronchi In more recent parenchymal lesions the diseased area is likely to show moth eaten margins Gumma in the lung may be visualized in the form of a cavity with fluid level A common finding is increased bronchovascular markings which radiate from the hilum in an arborescent pattern Enlargement of the hilar shadows is frequent in such cases There are cases where fibrosis which results from syphilis, shows an irregular or stellate appearance and not a linear one Discrete miliary nodular shadows caused by minute gummas may be found evenly distributed throughout both lung fields In some instances, miliary nodules are more marked on one side In other cases, a dense homogeneous shadow occupies one hemithorax The latter is decreased in size due to the underlying marked pulmonary and pleural fibrosis Simultaneously, one notes a displacement of the heart and other mediastinal structures toward the affected side, together with an upward shift of the corresponding diaphragm and compensatory emphysema in the form of increased radiotranslucency on the opposite side Complicating bronchiectasis can be readily recognized following the instillation of iodized oil The technique of this procedure is given in detail in the respective chapter Syphilitic pleural effusion is associated with the same type of x ray shadow as pleural effusions seen in other diseases When extensive fibrotic lesions are found at the time of the first examination, subsequent

serial films of the chest are not likely to reveal any change With this qualification, one can agree with the postulate of Allison, namely, that untreated lesions show a progression and adequately treated cases show a retrogression or disappearance of the disease on serially taken roentgenograms of the chest It is well to emphasize, however, in this connection the need for awareness of the fact that pulmonary lesions other than those caused by syphilis may disappear on specific treatment This may occur either as a matter of coincidence or as a favorable response to penicillin The postulate of Allison is more readily acceptable when specific treatment with bismuth and arsenicals is considered It is necessary to state at this time that predominantly fibrous lesions do not show appreciable improvement on antisyphilitic treatment For this reason, the latter cannot be used as a diagnostic criterion in such cases An important adjunct to the diagnosis of syphilis of the lung is x ray examination of the patient for evidence of aneurysm cor bovinum and skeletal changes of syphilitic origin in the chest or elsewhere

While serologic tests positive for syphilis do not necessarily mean syphilitic origin of the pulmonary disease in question positive serologic tests are a prerequisite of the diagnosis of syphilis of the lung In some instances, only the spinal fluid is found positive, in others a provocative injection of neoarsephenamine may be required to convert a negative serologic test into a positive one Another important item to remember is the possibility of biologically false positive serologic test This is known to occur after immunization following acute febrile respiratory diseases, including virus pneumonia also after measles lymphogranuloma venereum typhus, filariasis leprosy and Weil's disease and occasionally in lupus erythematosus, Hodgkin's disease and sarcoidosis

Concerning differential diagnosis, the following points must be kept in mind In all patients whose serologic test is positive for syphilis and who have an 'atypical' pulmonary disease which does not fit into known concepts of various affections such as tuberculosis, unresolved pneumonia, bronchopneumonia, bronchiectasis persistent bronchitis and others the possibility of the pulmonary involvement being of syphilitic origin must be considered The same attitude is advisable in patients with serologic reaction positive for syphilis

(1) When symptoms are less than would correspond to the extent of the pulmonary disease,

(2) When in the presence of demonstrable pulmonary disease, repeated examinations of the sputum, aspirated or lavaged bronchial secre

tions, or aspirated fasting gastric contents are negative for tubercle bacilli by direct smear, culture or guinea pig inoculation,

(3) When tuberculin tests with increasing strengths of tuberculin are negative,

(4) When other nontuberculous diseases of the lung can be ruled out with reasonable certainty This includes benign and malignant tumors, primary and metastatic, fungus infection, abscess, bronchiectasis pulmonary fibrosis due to infection, noxious dusts, fumes and gases, cardiac decompensation, atelectasis, sarcoidosis, infestation of the lung with animal parasites, and allergic diseases with pulmonary manifestations,

(5) When there is a prompt and favorable response to antisyphilitic treatment in the absence of other etiologically proved disease

Differential diagnostic orientation should be made relative to diseases the pulmonary manifestations of which cast widespread nodular shadows on the roentgenogram as seen in the case of bilateral miliary gummas There are a substantial number of such conditions, as outlined in connection with the discussion of pulmonary manifestations of lupus erythematosus

When pleural effusion occurs in association with syphilis of the lung it may be clear, serofibrinous, hemorrhagic or purulent Hemorrhagic effusion is more likely to be found than the other types Hemorrhagic pleural effusion, however, occurs in other diseases, such as carcinoma, thoracic lymphosarcoma lipoma and Hodgkin's disease, pulmonary infarction tuberculosis, early stage of streptococcal pleural infection, rheumatic fever, influenza of virus origin, pneumococcus pneumonia smallpox, typhoid fever, malaria, chronic nephritis, scurvy, Banti s disease, cirrhosis of the liver, massive atelectasis, including cases where the lung treated with artificial pneumothorax fails to reexpand

No one should consider the diagnosis of pulmonary syphilis an easy matter But if it is based upon the aforementioned determinants, it can be made with justification

Prognosis

The prognosis depends upon the time of detection in relation to the duration of the pulmonary involvement, upon the type of lesion, upon the extent of syphilitic processes in other organs, which if far advanced render the prognosis unfavorable and finally it depends upon the adequacy of treatment With the exception of very rare syphilitic pneumonias, pulmonary syphilis follows a slow, sluggish course On the other hand, under specific treatment, prompt regression of the pulmonary af

fection takes place, provided the lesion is not predominantly fibrotic in character It is interesting to observe how tumor like gummatous masses are rapidly reduced in size and then completely disappear during specific treatment In other instances slight linear fibrosis may remain at the site of the gumma Healing interstitial pneumonitis may leave behind linear peribronchial fibrosis Simultaneously with the clearing of the pulmonary lesion corresponding symptoms and signs disappear too Serologic tests may remain positive after the complete healing of the lung involvement Cor pulmonale is a grave consequence of extensive syphilitic pulmonary fibrosis For detailed discussion of this cardiac condition the reader is referred to the chapter on *Pulmonary Fibrosis*

Treatment

Early institution of specific measures is of utmost importance For this purpose one can resort to a combination of bismuth and neoarsphenamin or oxiphenarsine (mapharsen) in the form of alternating courses Meticulous care must be exercised in the technique of administration of these drugs Clinical experience shows that penicillin is quite potent in the treatment of this condition The usual course of penicillin treatment consists of the daily intramuscular administration of 300 000 units until 7 000 000 units have been given For congenital syphilis of the lung the total dose for the entire treatment should be 75 000 units per pound of body weight divided into corresponding single daily doses over a period of 15 days

Pleural effusion should be removed by repeated aspirations if necessary Symptomatic medication and measures for the patient s pulmonary and cardiac conditions are prescribed according to the requirements of the situation

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PULMONARY ANTHRAX

By ANDREW L BANYAI M D AND J WINTHROP PEABODY M D

Pulmonary manifestations of anthrax are caused by the Bacillus anthracis which is a spore bearing micro-organism and is capable of infecting cattle, sheep, horses and other animal particularly herbivorous ones and also human beings The pulmonary form of anthrax is brought about by inhalation of dust contaminated with the spores of this micro-organism This condition is most often seen in workers who handle hide horn wool hair bristles and bones of infected animals Also it occurs in sheep and cattle raisers shepherds farm laborers butchers and veterinarians Cases have been reported in stevedores and truck drivers handling raw hides in brush peddlers carpet weavers hardware store clerks in children playing on contaminated grounds and in persons washing contaminated clothes The pulmonary lesion is bronchitic or bronchopneumonic in character The bronchopneumonic process as well as the associated pleural effusion is often bilateral

The onset is acute, with chills high fever pronounced malaise prostration and dizziness Symptoms of coryza and conjunctivitis may be noted The chief complaints are excessive cough and expectoration of mucopurulent blood tinged or rusty sputum Also dyspnea cyanosis and thoracic pain are conspicuous The latter is caused by the involvement of the pleura, frequently with the formation of effusion

On physical examination impaired percussion note altered breath sounds increased voice conduction and numerous moist rales are heard over the involved areas of the lung Roentgenograms of the chest show irregular patchy densities usually together with findings characteristic of pleural effusion The diagnosis is based on the history of exposure the presence of typical skin lesion the severe clinical picture and on the isolation and identification of the causative micro-organism from the sputum or blood In this manner only is it possible to differentiate pleuropulmonary manifestations of anthrax from diseases due to other bacterial viral rickettsial or parasitic infections

Treatment

An expedient way to handle these patients is by the administration of adequate amounts of penicillin alone or with immune serum Penicillin is given in doses of 50 000 units intramuscularly every three hours night and day, or in a single daily dose of 300 000 units in aqueous solution with procaine If no satisfactory results are obtained in 24 hours one

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Treatment

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should resort to the administration of immune serum Of the latter, one should give from 200 to 500 cc intravenously, *repeating the dose at 12* hour intervals for three doses, and follow it with smaller doses once a day, as required by the patient s condition It is mandatory to observe every precaution for the prevention of anaphylactic reaction in connection with the use of immune serum

In severe cases, penicillin is administered by the intravenous drip method For this purpose, the solution is prepared by dissolving the dry powder of sodium penicillin in isotonic solution of sodium chloride or in 5 per cent dextrose solution in triple distilled water The contents of one vial (100,000 units) are dissolved in 1,000 cc of the solvent An 18 gage Lewisohn needle is inserted deeply into a vein and anchored with adhesive tape The arm selected for the injection is immobilized in a suitable position on a simple padded splint *The flow of the penicillin solution* is set to 30 drops per minute Following the continuous administration of penicillin in this manner during the *first 24 hours intramuscular* injections are given in doses of 50,000 units of penicillin every three hours around the clock

Also aureomycin and terramycin are effective in the treatment of anthrax when given orally in doses of 100 mg per Kg of body weight per day for five to seven days Gold reported eight cases of anthrax successfully treated with aureomycin, chloromycetin and terramycin, with no untoward effects, excepting aureomycin which caused intense nausea and vomiting All these patients were treated at home Clark treated four cases successfully with chloromycetin

Prior to the use of penicillin terramycin and aureomycin, satisfactory therapeutic response was observed from the use of sulfonamides in combination with immune serum

General supportive measures are applied according to the individual requirements of the patient Pertinent details are outlined in the chapter on Pneumonia

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PULMONARY GLANDERS

By ANDREW L. BANYAI, M.D. AND J. WINTHROP PEABODY, M.D.

Glanders (malleus) is an infectious disease rarely seen in man. It is caused by the Malleomyces mallei (Pfeifferella mallei) and contracted from diseased horses and mules. The micro-organism is a gram negative bacillus somewhat shorter and wider than the tubercle bacillus. The disease is only very rarely seen in this country due to well organized preventive veterinary measures. Its pathogenic micro-organisms are transmitted through direct contact with diseased animals in which the condition manifests itself in the form of purulent rhinorrhea associated with ulcers of the nasal mucosa or in the form of ulcers of the skin. Another source of infection, sporadically reported in this country, is laboratory material containing Malleomyces mallei.

There are two types of the disease, acute and chronic in human beings. The incubation period varies from three days to three weeks. Following this, the patient becomes seriously ill with chills, high fever and marked prostration. Headache, dizziness, blurred vision, photophobia, nausea and pain in the muscles, muscle tendons and joints are conspicuous symptoms. Vomiting and diarrhea are common. The most characteristic manifestation of the disease is the development of ulcerous lesions on the nasal mucous membrane associated with swelling and erythema of the nose and with purulent, foul nasal discharge. These changes are accompanied by similar lesions in the larynx and the tracheobronchial tract. Pulmonary involvement is characterized by severe ulcerous tracheobronchitis and bronchopenumonia or lobar pneumonia. In such instances the patient complains of excessive cough with mucopurulent, blood-tinged expectoration. The findings on physical and roentgenologic examinations are not typical but correspond to the underlying pulmonary lesion.

Other findings which are of value in establishing the diagnosis are: 1. The formation of pustules in the skin which may become confluent and occupy large areas. Following the rupture of these pustules numerous small ulcers become visible. 2. Nodular infiltration of the collateral lymphatics and the regional lymph nodes in the neck and in the vicinity of the skin lesions. 3. Development of abscesses in the large muscles. Conclusive diagnostic finding is the identification of Bacillus mallei in the pus or sputum, or its isolation by guinea pig inoculation or culture from the blood or from purulent material from superficial ulcers or deep abscesses.

Other laboratory findings may offer corroborative evidence Complement fixation test is considered positive with serum diluted to 1 20 or higher The agglutination test is considered confirmatory when its titer is higher than 1 320 Intracutaneous test is done with 0 1 cubic centimeter of the 1 10,000 dilution of commercially available mallein The test is read from 24 to 48 hours after an intracutaneous injection A positive reaction shows an erythema from 10 to 20 millimeter in diameter The skin sensitiveness to mallein may persist for years after recovery from the disease Negative mallein skin test does not rule out glanders

Hematologic examinations reveal normal blood count or leucopenia with relative lymphocytosis

Roentgenograms of the chest show more or less circumscribed bronchopneumonia or a well delineated lobar pneumonia

Concerning differential diagnosis, one should keep in mind virus pneumonia, infectious mononucleosis, lung abscess, lobar pneumonia and bronchopneumonia of bacterial, rickettsial viral or parasitic origin

Acute glanders has a grave prognosis, with a high mortality rate Death ensues in from ten to thirty days In patients with mild infection and with subacute or chronic form of the disease, resolution of the pulmonary infiltration takes place in from two to three months The accompanying fever may subside in a week or two Recurrence of symptoms may occur a few weeks after an apparent recovery

Treatment consists of the administration of streptomycin or sulfadiazine in addition to the necessary general supportive measures Streptomycin is given in doses of 1 to 2 Gm daily, administered intramuscularly The initial dose of sulfadiazine is 4 Gm (60 grains) followed by 1 Gm (15 grains) every four hours In severe cases it is preferable to give 5 Gm (75 grains) of sulfadiazine in 1,000 cubic centimeter of isotonic solution of sodium chloride intravenously and follow it with the oral administration of the drug according to the aforementioned schedule

MELIOIDOSIS

By Andrew L. Banyai, M.D. and J. Winthrop Peabody, M.D.

This condition is encountered in Indo China, Thailand, Burma, Federated Malay States, East Indian Islands and Ceylon. The largest number of instances, a group of 200, was reported by Krishnaswami of Rangoon. An American soldier's case was recorded by Cox and Arbogast, a British soldier's case by Grant and Barwell and that of a South African by Mayer and Finlayson. The first case of melioidosis occurring in the United States was observed by McDowell and Varney. Mirick and his associates reported two fatal cases of American military personnel on the island of Guam. The disease affects rats, rabbits, cats, dogs, rarely horses. It is caused by the Malleomyces pseudomallei (Pfeifferella whitmori), a gram-negative non acid fast, motile micro organism which is from 2 to 6 microns in length and shows bipolar staining. It is transmitted by contaminated food, water or by the bite of the mosquito, Aedes aegypti, and the rat flea, Xenopsylla cheopsis. Melioidosis is known to occur in acute and chronic forms.

Characteristic pathologic findings in the lungs have been accurately described by Mirick and his associates. "The pulmonary lesions consisted of widely distributed miliary abscesses, often lying discretely under the pleura or more deeply in the lung parenchyma and sometimes coalescing into large zones of suppuration. The intervening pulmonary tissue was the seat of an ordinary acute pneumonitis, with fibrin and neutrophilic leucocytes as the chief components of the exudate. Where the abscess broke into the bronchioles the latter had their mucosal epithelium desquamated and their lumens filled with purulent material. The larger bronchi, and even the trachea were partially ulcerated, and suppuration replaced parts of the mucosa and submucosa. The distinctive feature of the pulmonary infection, as it was of the other viscera involved, was the granulomatous nature of the lesion. Except for the most acute miliary abscesses, the usual focus of infection had a definite wall of fibrin either partially or extensively organized. The "core" of the lesions was composed of either liquefactive coagulative or caseous necrosis, sometimes one and sometimes another. These small granulomas were reminiscent of tubercles or of the lesions of glanders or tularemia, depending on the type of necrosis and the amount of organization by granulation tissue. In the lungs, where the pathologic process was most extensive, it had a certain resemblance to changes caused by actinomycosis."

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CHAPTER VII

TROPICAL AND PARASITIC DISEASES OF THE LUNG

RESPIRATORY DISEASES IN THE TROPICS

By R VISWANATHAN, M D

DISEASES of the respiratory system are as common, if not more, in the tropical countries, as they are in other parts of the world Excessive humidity of the atmosphere over the greater part of tropical regions particularly in the coastal belts, torrential rains in many areas, low standard of nutrition of the population particularly vitamin A deficiency *which make respiratory epithelium more susceptible to infection*, and certain protozoal and helminthic infections peculiar to the tropics are perhaps some of the contributing factors in the high incidence of respiratory diseases in this part of the world

Respiratory diseases in the tropics fall into two categories namely, those which are cosmopolitan and those which are prevalent only, or more common, in the tropics

MALARIA

According to Manson, pulmonary forms of subtertian malaria characterized by bronchitis, pneumonia and pleurisy, especially on the left side, and often associated with myocarditis, have been recognized clinically Diagnosis in these cases has been made by the finding of malarial parasites in the blood

During the last war cases of pneumonitis during the course of malarial pyrexia have also been reported

Strong speaks of the pneumonic type of malaria, in which some symptoms of bronchopneumonia, an element of periodicity, and response to quinine have been observed

Applebaum and Shrager have tabulated 113 cases of pneumonitis with malaria, of which six only were of the lobar type One of them was sulpha drug resistant and responded to antimalarial therapy

Heilig and Sharma have reported six cases of pneumonia with malaria which did not respond to sulpha drugs but responded rapidly to antimalarials According to them an ordinary lobar pneumonia probably caused by pneumococci, is rendered sulpha-drug and penicillin resistant by a co existant malarial infection The malarial parasite and the humoral changes produced by it prevent the normal response to the standard treatment, resolution and defervescence are delayed indefinitely unless and until the malarial factor is eradicated

The writer has seen a number of cases of pulmonary eosinophilosis coexisting with malaria In fact eosinophilosis was detected during routine examination of blood in cases admitted for malaria

There is not enough evidence to show that plasmodium of malaria can by itself produce pulmonary symptoms

Whatever be the nature of pulmonary involvement during the course of malaria, antimalarial treatment should be instituted along with routine treatment for the pulmonary lesion

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FILARIASIS

Certain pathological conditions are produced in human beings by filaria which live in the lymphatics and connective tissues Live embryos, called microfilariae, are produced by these adult worms and are found commonly in the bloodstream The microfilaria disappear from the blood during certain parts of the day It has been found that, during their diurnal temporary absence from the peripheral circulation, the microfilaria are commonly in the lung capillaries Transient pulmonary infiltrations resulting from the presence of microfilariae in the lungs have been reported At the time when these infiltrations occur cough and bronchial spasm are frequently seen They are associated with eosinophilia in the blood Such pulmonary manifestations in filariasis are probably due to allergy

Culbertson and his associates used neostibosan a pentavalent antimony preparation successfully for the treatment of filariasis

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KALA AZAR

Kala azar is a disease which occurs in endemic as well as in epidemic forms in certain tropical and subtropical countries and is characterized by prolonged pyrexia, enlargement of spleen and liver and pigmentation of the skin It is due to infection with a protozoal organism called Leishmania donovani

Respiratory system in this disease is very prone to inflamation There is an irritating cough at all stages of the disease without much physical signs The cough may be so distressing and severe as to interfere with sleep It is common to find basal pulmonary congestion in the later stage In severe forms bronchopneumonia is a frequent complication

Treatment consists of the intravenous administration of sodium or potassium antimony tartrate or neostibosan a pentavalent antimony compound

Tsutsugamushi Disease

Known by various names like Japanese River Fever, Mite Typhus Scrub Typhus, etc, Tsutsugamushi Fever is an acute infectious disease of the typhus group characterized by fever of 15 to 20 days duration and eschar associated with local adenitis and a maculo papular rash and occasional deafness

It is caused by Rickettsia orientalis the transmission being from infected rats to man by the bite of certain larval mites

The disease assumed epidemic proportions during the last war, particularly in Burma, Malaya and the Southwest Pacific where the Allied troops were fighting the Japanese

In this disease the respiratory system is very commonly affected Cough is a common symptom in the early stages of the disease, moist rales and rhonchi being frequently noted Signs in the lungs begin to appear from the seventh day They are however transient in mild cases whereas in the more malignant cases signs of bronchopneumonia are frequently present Increased respiratory rate and cyanosis of the lips are frequent in these cases Cough is irritating with tenacious, blood streaked,

frothy sputum The signs disappear by the end of the third week in the cases which recover

Recent trials with chloromycetin, aureomycin, terramycin, para aminobenzoic acid and combined streptomycin sulphadiazine therapy have given very promising results

PULMONARY SCHISTOSOMIASIS

Bilharzial involvement of the lungs has been recognized for many years Belleli in 1885 was the first to record the presence of schistosome ova in the lungs Symmers showed in 1905 the presence of adult worms in the blood vessels of the lungs Turner in 1909 found ova in the lungs in 50 per cent of necropsies in South Africa Shaw and Ghareeb gave a full account in 1938 of the pathology of the disease and stated that about 2 per cent of those affected with bilharziasis die from pulmonary involvement *According to them schistosomiasis in Egypt is the com* monest cause of Ayerza s disease, which may result either from S mansoni or S haematobium Galfand, however, working in Rhodesia has not been able to confirm this observation in a series of autopsies

According to Erfan 60 to 70 per cent of the inhabitants in Egypt are infected with schistosomes, at least 33 per cent of these have pulmonary schistosomiasis According to him males are more affected than females The disease is most common in children and young adults, the highest incidence being between 10 and 30 years

Deposition of schistosome ova and worms is the direct cause of pulmonary lesions These reach the lungs through the blood stream from the urinary and intestinal tracts After reaching the lungs the ova get obstructed in the small arterioles and pass through their walls and lie outside them The tissue reaction around the ovum results in the formation of the bilharzial tubercle, composed of histiocytes and eosinophil leucocytes Later, lymphocytes and one or more giant cells appear Scar formation occurs in the tubercle when it is invaded by fibroblasts

The bilharzial tubercle appear as miliary nodules on the cut surface of the lungs The pulmonary artery and its primary branches get dilated and may reach aneurysmal size Their walls may show atheromatous changes The right ventricle is usually dilated and hypertrophied

The adult worms while living are harmless, but when dead they produce a focal pneumonia with necrosis

Clinically two forms of the disease are recognized, broncho-pulmonary and cardiovascular The broncho-pulmonary type manifests

itself in the form of asthma, bronchitis, pulmonary emphysema and fibrosis. The cardiovascular form exhibits symptoms similar to those of Ayerza's disease.

Radiologically in the early stages, small branches of the pulmonary artery show nodules. At a later stage the nodules are more numerous and hilar shadows are increased in size. In the advanced stage typical cor pulmonale can be seen. *Presence of ova in the sputum will clinch* the diagnosis of pulmonary schistosomiasis. *As, however, ova are not commonly seen in the sputum*, diagnosis has to be made by the demonstration of ova in urine or faeces, particularly when pulmonary signs and symptoms are present.

Treatment consists of the early administration of antimony compounds. Azmy advocates rectal injection of tartar emetic as treatment. Khalil uses fuadin. Emetine has been recommended by Maciel.

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PARAGONIMIASIS (ENDEMIC HAEMOPTYSIS)

Infection with Paragonimus Westermani produces pulmonary symptoms and rusty brown sputum in which the characteristic eggs are present.

The disease is found in Japan, Korea, China, Malay, the Philippines, the East Indies, Indo China, Burma and some parts of India.

Infection of man occurs as a result of consumption of infected crabs or cray fish which serve as the second intermediate host, the first being a snail. Infection of the intermediate hosts is by the ova of parents thrown out in the sputum. *On reaching water the eggs hatch in four* to seven weeks and the miracidium enters a snail and undergoes a developmental change ultimately forming cercariae. The cercariae

escape into water and bore their way into certain species of cray fish When man swallows the cray fish the cyst wall is digested in the stomach and the adolescent cercaria traverses the abdominal cavity, penetrates the pleura and lungs and ultimately reaches the bronchioles where it settles down in a cyst cavity

Many small cysts of a deep colour containing the parasites are found in the lungs The flukes are often found in burrows or tunnels the wall of which are formed of connective tissue Cavities resembling bronchiectasis may be formed by the breaking down of adjacent tunnel walls Musgraves has described four types of lesions namely

(1) Nonsupperative areas containing eggs with round cell and connective tissue formation

(2) Tubercle-like lesions

(3) Suppurative lesions

(4) Ulcerative lesions in which the healing is only partial

It has been found that the fluke infects not only the lung but also organs such as the liver, intestines, lymph glands, muscles, testes and brain

The symptoms are those of chronic bronchitis Cough is associated with expectoration of gelatinous reddish sputum Remissions are common The disease usually lasts for years Recurring attacks of haemoptysis without the presence of other known causes, and presence of characteristic eggs in the sputum enable one to make diagnosis of paragonimiasis

Tillman and Phillips while reporting 12 cases of paroganimiasis among 250 patients admitted for observation for tuberculosis, point out that paragonimiasis may simulate tuberculosis closely so that the former should be considered in the differential diagnosis of haemoptysis in those who have been in endemic regions

By way of treatment, Kobayashi has recommended 1 25 c c of 2 per cent solution of emetine hydrochloride intramuscularly four times a day for five days Yokogawa has reported good results with prontosil

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PNEUMONIC PLAGUE

Pneumonic plague is a highly fatal disease It occurs frequently among the marmot trappers of Northern China, who live under in sanitary conditions Owing to the multitude of bacilli found in the sputum it is very dangerous to all those who go near the patient In the early stages, congestion and oedema of the infected lungs are found Later on pneumonic consolidation with blood stained pleural effusion sets in

The onset is sudden with rigor, fever, intense headache, vomiting, and prostration Later, cough and dyspnoea accompanied by profuse, blood stained, watery sputum set in Cloudy consciousness and delirium are invariably premonitary of impending fatal termination The patient usually dies in four or five days This is the most fatal form of plague

Until recently no form of treatment used to be of any avail The reported recovery of a case, by Huang *et al*, through treatment with streptomycin and sulphadiazine holds out hope in this extremely fatal condition

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PULMONARY EOSINOPHILOSIS

Introduction

Pulmonary eosinophilosis is a clinical condition characterized chiefly by cough paroxysms of dyspnoea, persistent and absolute eosinophilia, a raised total white cell count, and frequent systemic manifestations such as fever, lassitude, and loss of weight It is only within the last 10 or 15 years that this syndrome has been recognized as a separate entity In 1935 a case was referred to the writer as one of miliary tuberculosis, because of a high remittent type of fever, cough, and typical disseminated shadows in the radiograph of the lung The sputum did not contain tubercle bacilli Blood examination, however, showed massive eosinophilia and high leucocytosis The condition ran a benign course, though it took over nine months for all the symptoms to clear Later, some more cases of a similar nature were seen by the writer and a note describing them was published in the annual report of the King George Hospital, Vizagapatam (India) for 1939

Aetiological Factors

Six hundred and eighty-five cases conforming to the description of this clinical condition, though under different names, have been reported in the medical literature during recent years Inquiries made by the writer from several medical men and women in different parts of India go to confirm the impression that many more cases of pulmonary eosinophilosis have been observed by general practitioners Most of the recorded cases have been from India and Ceylon A few, however, have been reported from America, England, North Africa, Tanganyika, China, Australia, Singapore, and Southwest Pacific Islands Weingarten (1943) thought the disease was confined to the coastal districts of India Other reports, however, show that it is widely distributed throughout the country It has occurred among people from places as widely separated as Delhi, Nagpur, Lahore and Peshawar Many of these patients have never been to the sea coast at any time in their lives As in the majority of cases the onset or the exacerbation of the disease occurs during the rainy season, or soon after the rains, it is possible that the humidity of the atmosphere, rather than nearness to the sea, might be a contributing aetiological factor in the disease It cannot be considered exclusively as a tropical disease as a few cases have been reported from other parts of the world

The disease has been observed at all ages from 1 to 62 The highest incidence in all the reported series has been in the 20 to 40 age grou There is a preponderance of males over females in all the report series All races appear to be affected There does not seem to be a constitutional or familial susceptibility Occupation does not appe to bear any aetiological relationship, nor does the economic status of th individual Reports from Ceylon (Carter, *et al*, 1944) and recen reports from Bombay (Jhatakia, 1946) suggest, however, that there is a high incidence of the disease among workers in grain stores

Ceylon workers (Carter, *et al*, 1944) have found mites in the spu tum in a large percentage of cases with respiratory symptoms There are, however, some outstanding difficulties in accepting the mite as the causative factor in pulmonary eosinophilosis In the first place, the majority of cases, in which the Ceylon workers found mites in the sputum did not have high eosinophilia which is essential diagnostic criterion for the disease Secondly, many other workers, have failed to find mites in the sputum of patients suffering from the disease Thirdly, as o writer aptly puts it, it will be very difficult apart from tech

siderations, to prove mite infestation of the respiratory tract in cases showing lung symptoms but unproductive cough Fourthly, typical cases have recently been reported without cough or asthmatic attacks, but conforming otherwise to the symptomatology of the disease, and showing favorable therapeutic response to arsenic (Treu, 1944, Jhatakia, 1946)

Pathology

The pathology of the condition is obscure The writer had the unique opportunity of studying the postmortem appearances in a case of pulmonary eosinophilosis that died of arsenical encephelopathy during the course of treatment Histologically areas of interstitial fibroblastic proliferation with alveoli lined with swollen cells and their lumina filled with phagocytic cells chiefly eosinophiles were seen These partially consolidated areas were closely related to the terminal bronchioles In some areas of the lung, characteristic nodules containing large giant cells in the center and mononuclear cells at the periphery were seen They were definitely unlike the giant cell system found in tuberculosis The histological changes suggest that the infection is probably by inhalation and that the infecting agent gets into the peribronchial tissue and sets up an inflamatory process, with discrete scattered areas of cellular infiltration, monocytic and eosinophilic



Fig 1 Photomicrograph of lung from case of pulmonary eosenophilosis that died as a result of arsenical encaphalopathy Note Nodule in the center with a group of giant cells surrounded by monocytes (low power)

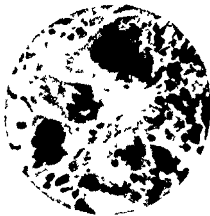


Fig 2 Center of the nodule shown in Fig 1 under high power magnification showing the giant cells

Symptomatology

Table I gives symptomatology in 207 cases studied by the writer

Study of the clinical course of the disease suggests the existence of two distinct types, namely, the acute and the chronic The acute type can again be subdivided into (1) the self limiting type in which the condition clears up completely within a short period without treatment, and (2) the type in which the disease goes on to the chronic stage if untreated The vast majority of cases reported so far belong to the chronic variety

Acute Type

In the acute type, the onset is sudden with high fever ranging from 102° to 104° F cough and rapid respiration, simulating an attack of acute bronchiolitis or pneumonia Physical signs as a rule are those of acute bronchitis In a few cases, however, signs of patchy consolidation are detected Only the presence of absolute eosinophilia helps to reveal the true nature of the condition In about twenty five per cent of the cases the symptoms clear up completely without any specific treatment in four to six weeks The others, however pass on to the chronic stage

Chronic Type

In the ordinary chronic variety the mode of onset is gradual General malaise, lassitude impaired appetite and a low grade fever ranging from 99° to 101° F are the usual presenting symptoms After a week or 10 days the patient begins to have a dry cough In a good number of cases, however, cough is the first symptom to be noticed The cough is hacking and unproductive in the early stages It comes on in paroxysms particularly at night After a month or two the patient begins to cough up a scanty amount of viscid sputum A fit of coughing continues until a pellet of viscid mucus is brought up Sooner or later the patient begins to feel breathless either after a paroxysm of cough or after any kind of physical exertion Breathlessness is a more frequent manifestation of the disease than asthmatic attack Paroxysms of expiratory dyspnoea no doubt occur in a large number of cases Such cases are often mistaken for true asthma In an untreated case of the chronic variety, the febrile period varies from a few days to two months while the respiratory symptoms last for a year or more In some cases, the disease continues for years in the form of periodic attacks of asthma-like paroxysms

Signs

Physical signs in the lungs are absent during the first few weeks Later on when the cough becomes productive, moist rales and rhonchi are heard at the base of both lungs When there is an asthmatic paroxysm prolonged expiration and sonorous and cooing rhonchi are heard *Hyperresonance of the chest* is a frequent finding in the later stages Enlargement of the spleen is found in about 50 per cent of the cases particularly during the febrile period

The sputum rarely contains Charcot Leyden crystals or Curschmann s spirals, but clumps of eosinophils are frequently seen

Atypical Cases

A few atypical cases, with presenting symptoms like prolonged pyrexia exhaustion, palpitation, precordial pain, lymphatic glandular enlargement and *enlargement of liver occurring singly or in combination* with respiratory symptoms have been reported The diagnosis is made in these cases *by the finding of high eosinophilia and their therapeutic* response to arsenic

Laboratory Findings

The changes in the blood are the most characteristic feature of the disease The total white cell count varies from 12,000 to 80,000 per cmm while the eosinophil percentage ranges between 20 and 80 Massive eosinophilia is responsible for the high leucocytosis The absolute count of the neutrophils remains more or less constant Immature eosinophils *are rarely seen*, while hypermature ones are more frequently met with Two types of eosinophils one with well stained coarse granules, and the other with lightly stained *fine granules*, are seen *with equal frequency* The clinical significance of the two types is not understood The degree of eosinophilia bears no relationship to the severity of the symptoms The bone marrow shows preponderance of mature eosinophils Myelocytic reaction is absent As a rule the pulmonary signs and symptoms disappear more quickly in response to treatment than the alterations in the blood

Viswanathan and Natrajan (1945) have shown that the serum of most of the cases produced high titre cold agglutination of red blood cells *Subsequent to the publication of their results* 52 more sera were tested by them Forty out of the 52 gave high titre cold agglutination A

larger percentage of positive results was claimed by Lal in a personal communication

D'Abrera (1946) and Menon (1946) found positive Wassermann and/or Kahn reactions in some of their cases in the absence of any positive evidence of syphilis Menon (1946) uses the test as one of the diagnostic criteria, particularly when the serological reactions are reversed after oral administration of stovarsol

In the majority of the cases the erythrocyte sedimentation rate is raised

Radiographic Findings

The so called typical x ray picture of disseminated mottled shadows distributed throughout both lungs is not a consistantly observed phenomenon The mottling may be confined to one lung or part of one lung Since it may be present only in certain phases of the disease, x-ray pictures taken at other times may not show any changes which can be considered typical of the condition In some cases, however, the shadows are so uniformly distributed as to suggest a haematogenous dissemination X-ray changes are commonly seen during the febrile stage of the disease During the later stages prominent bronchial markings only are found In a fair proportion of untreated cases, however, the x ray shadows persist for months

Diagnosis

A history of an illness with febrile onset and long continued cough, breathlessness on exertion, fits of bronchial spasm, massive eosinophilia in the blood with a high total white cell count and mottled shadows in the radiograph of the lungs is sufficient evidence to establish a diagnosis of pulmonary eosinophilosis Other conditions producing eosinophilia have to be considered for purposes of differential diagnosis Helminthic infections can be excluded by systematic examination of stools or by therapeutic elimination of the possibility Difficulty might arise when a case of true asthma with eosinophilia is encountered In asthma however the total white cell count is rarely above normal, though in some cases there may be a relative eosinophilia Radiography of the chest does not show any of the characteristic abnormalities Normal erythrocyte sedimentation rate and negative Wassermann test will also help in the diagnosis Asthmatic attacks are rarely relieved by arsenical injections On the other hand the therapeutic response of pulmonary eosinophilosis to arsenicals is nothing short of dramatic

Loeffler's syndrome is another important condition from which pulmonary eosinophilosis has to be differentiated Some writers are even of opinion that the conditions are identical Loeffler (1936) described the syndrome as characterized by transitory migratory pulmonary infiltration associated with peripheral eosinophilia and paucity or absence of systemic manifestations He was at first of opinion that it was a tuberculous process Later, he produced evidence to show that it was due to the pulmonary phase of Ascaris infection Engel (1937) ascribed it to inhalation of pollen from the privet shrub Meyer (1937) thought that pollen of Convallaria in Europe was the offending factor Markey (1943) has recently reported on Loeffler's pneumonia in asthmatic states. Ascaris taenia saginata, trichuris trichiura, fasciola hepatica, entamoeba histolytica, brucellas and azosulphamide have all been incriminated for its causation Wright and Gold (1946) add cutaneous helminths as an additional cause Evidently Loeffler's syndrome is an allergic response to a variety of allergens Absence of systemic disturbances transitory and migratory pulmonary infiltrations rapidly fluctuating blood changes spontaneous disappearance of all signs without treatment, negative Wassermann test and normal sedimentation rate will enable it to be differentiated from pulmonary eosinophilosis

Prognosis

If untreated pulmonary eosinophilosis persists for months, sometimes years with remissions and exacerbations Arsenic acts as a specific in the great majority of cases and response to it can be used as a diagnostic criterion A few cases however (less than 2 per cent) do not respond fully to treatment though some amelioration of symptoms is obtained in all Also a few cases show relapses but most of these respond to a second or sometimes, a third course of treatment The disease of itself has not up to-date produced any reported death

Treatment

A few medical practioners in India had been in the habit of using preparations of arsenic such as soamin and neoarsphenamine, and claiming dramatic results long before pulmonary eosinophilosis was recognized as a clinical entity The cases of asthma that were cured by them were evidently cases of the latter condition and not true asthma A course ordinarily consists of eight weekly injections, beginning with an initial injection of 0 15 Gm and continuing with 0 3 Gm for subsequent ones In milder cases a short course of four injections is found

to be sufficient. Some writers claim successful results with oral administration of stovarsol or carbarsone.

Discussion

Pathogenesis of pulmonary eosinophilosis has been a debated matter so far. Widely divergent views have been expressed regarding the nature of the condition. The confusing situation can, however, be clarified by providing answers to the two following questions, namely

(1) Can we consider this symptom-complex as a distinct clinical entity?

(2) Is it infective or an allergic process?

As regards the first question the answer is in the affirmative. It is no doubt true that eosinophilia occurs in a variety of conditions such as intestinal helminthiasis, hydatid disease, skin disease, Hodgkin's disease, periarteritis nodosa, urticaria, asthma, and certain infectious diseases like scarlet fever. Massive eosinophilia has also been found in cases of trichiniasis, and in some cases of filariasis. A combination of transient pulmonary infiltrations with high eosinophilia is also found in all those conditions which are included under the generic name of Loeffler's syndrome. Pulmonary eosinophilosis cannot be included in any of these categories because of the consistently occurring combination of symptoms of fever, loss of weight, cough, breathlessness, asthmatic attacks, associated with signs of pulmonary infiltrations, and persistent massive eosinophilia. Pulmonary eosinophilosis is, therefore, a distinct clinical entity.

The second important question is whether pulmonary eosinophilosis is an infective process due to a specific, arsenic sensitive, organism, or whether it is an allergic manifestation in response to different allergens.

Eosinophilia and asthmatic attacks are the points put forward in favor of allergic origin. Ratner (1942) is of the opinion that leucopenia is so characteristic of true serum sickness, serum allergy, protracted anaphylaxis, and drug allergy, that a fall in white cell count can be considered as almost pathognomonic of allergy. While leucopenia occurs in the early stages, eosinophilia is characteristic of the chronic oft repeated expressions of allergy. In his opinion eosinophilia is never manifested in the early allergic phase. If the symptom complex of pulmonary eosinophilosis is an allergic response, there should be no eosinophilia in its early stages. Cases of sudden onset with no previous history of any type of allergic manifestations were found to have massive

eosinophilia from the beginning It is also said that during the allergic phase as for instance in the beginning of an asthmatic attack there is a sudden fall in the white cell count as well as in the eosinophil percentage In pulmonary eosinophilosis on the other hand both are usually raised during an exacerbation

Experimental work of Menon (1946) affords confirmation of the assumption that pulmonary eosinophilosis is not an allergic response Injection of blood from a patient into a guinea pig produced initial eosinophilia and secondary leucocytosis in ten days He argues that the changes are not due to anaphylaxis because *only one injection of blood* was given and leucopenia and not leucocytosis is the usual finding in hypersensitive states He assumes that the blood of the patient contains material which is responsible for these changes on animal inoculation

In five cases of accidental death among soldiers who were apparently *in good health* Meyenburg (*1946*) found eosinophilic infiltrations and giant cells with multiple nuclei in the lungs He also noted eosinophilic bronchitis and eosinophilic bronchiolitis He concluded that Loeffler s *infiltrations may be real eosinophilic bronchopneumonias originating* from bronchogenic infection Meyenburg s cases were in all probability cases of pulmonary eosinophilosis

Peribronchial lesions with eosinophilic infiltration of the interstitial tissue and some alveoli and the presence of giant cell nodules in relation to the bronchioles seen in the lungs of the cases reported in the preceding pages are suggestive of a bronchogenic infective process

A positive Wassermann reaction obtained in many cases of tropical eosinophilia both by Menon and D Abrera and Stork with reversal of serologic findings *after arsenic medication is also in favour of infec*tion with an arsenic sensitive organism

The findings by the Ceylon workers and by Van Der Sar of mites in the sputum of patients with asthmatic symptoms and eosinophilia has given rise to the speculation that mite infestation of the respiratory tract is the cause of pulmonary eosinophilosis Carter and D Abrera have produced in Toque monkeys irregular spasmodic cough and fluctuating eosinophilia by intratracheal introduction of mites As against this theory of mite infection are the negative findings of most other writers There is *of course the possibility of* a mite borne organism and not the mite itself being the causative factor The mite is a vector for other diseases such as typhus It is possible that *the organism of eosinophilosis*

is also carried by mites and introduced through the respiratory tract or through the skin. It would be unprofitable to speculate on the nature of the organism without definite evidence. Viswanathan (1945) drew a parallel between this condition and atypical pneumonia by the finding of high titre cold agglutination along with pulmonary infiltration in both the conditions. Since atypical pneumonia is considered to be due to a virus infection, can pulmonary eosinophilosis also be a virus disease?

TABLE I
PULMONARY EOSINOPHILOSIS
SYMPTOMATOLOGY IN 207 CASES

		No. of Cases	Percentage
1	Cough	201	98.1
2	Lassitude	182	88.6
3	Breathlessness on exertion	176	85.02
4	Loss of weight	113	54.5
5	Fever low intermittent	91	43.9
6	Fever high remittent	6	2.6
7	Fever high continuous	5	2.4
8	Asthma	56	27.05
9	Heaviness and pain in chest	26	12.5
10	Haemoptysis	9	4.3
11	Palpitation	6	2.08
12	Enlargement of spleen	74	35.7
13	Enlarged glands	2	0.9
14	Eosinophiles above 2,500	196	95.7
15	Eosinophiles above 10,000	102	48.6
16	Positive x ray findings	105	50.7
17	Raised erythrocyte sedimentation rate	64 / Total 85 done	75.2
18	High titre cold agglutination	103 / Total 135 done	76.2
19	Positive Wassermann test	32 / Total 65 done	49.2
20	Positive Paul Bunnell test	3 / Total 9 done	33.3

During the last two years, the writer has conducted histological studies of lungs and brain of guinea pigs into which blood of patients suffering from pulmonary eosinophilosis was injected intraperitoneally or intranasally. In most of the animals lung sections showed spasm of the smaller bronchioles, and peribronchial and interstitial infiltration with eosinophiles, lymphocytes and a few polymorphs. The brain sections

showed meningeal reaction in certain places, and perivascular lymphocytic cuffing around some of the capillaries These changes were not found in the controls There is therefore, sufficient evidence to suggest the possibility of the aetiological agent in pulmonary eosinophilosis being a virus Further work is no doubt required to confirm the theory and for the isolation of the infecting agent

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PULMONARY AMEBIASIS

By Donato G Alarcon M D

Amebic dysentery is a disease found in all latitudes although it is more often endemic in temperate regions as well as in the tropical climates where it particularly afflicts the communities with deficient hygienic conditions Regardless of these circumstances, however outbreaks of epidemic amebic dysentery have been reported in northern cities which have a higher standard of sanitation One of the recent instances was the outbreak of Chicago not many years ago Epidemics have been reported in regions as septentrional as the Kola Peninsula

Craig estimates that around 5 to 10 per cent of the people of the United States are infected with Endamoeba histolytica It is reasonable to expect that the prevalence in the years following the second World War should be high since a great number of people returning from Asia are probably cyst carriers

In other countries the prevalence is excessively high and it is a sound principle to think of amebiasis and investigate accordingly in any person provenient from any tropical or subtropical climate Too many people from these regions are cyst carriers whether or not they are aware of having suffered dysentery The life cycle of the Endamoeba has three stages one is the vegetative stage found during the acute attacks the second is the precystic stage and the third is the cystic stage, its resistant form which permits the parasite to survive in the host for many years It is important to point out that only in the cystic stage is amebiasis transmissible and that the ingestion of the vegetative form does not cause the disease on account of the destructive action of the gastric juice on the amoeba Therefore the cyst carriers are the ones who may spread the disease although they can be apparently healthy If these carriers are handling food and are therefore able to contaminate it, the potential risk of their contact is readily understood The fecal pollution of green vegetables is also very important and other carriers besides the human convalescents must be kept in mind Flies are among the carriers most responsible for the spread in epidemic as it is known (Craig) that the amebic cysts can survive for as long as 48 hours in the intestine of the flies

Even in cities where the water is adequately chlorinated this fluid is not considered safe from amebic contamination because the cysts resist the conventional chlorination It is believed that to obtain the destruc-

paratyphoid infections, brucellosis, malaria, tuberculosis, and pyogenic infections

The symptoms most frequently found are as follows

Cough This is a constant symptom At the early stage it is dry or the expectoration is scant mucous or slightly purulent

Expectoration Strawberry jelly like or chocolate like sputum is not found in the beginning It indicates an advanced abscess draining through a bronchus

Pain The right basal region posteriorly or anteriorly is its frequent site This pain is persistent, moderate and may radiate to the shoulder or the neck

The appearance of the patient is impressive because the very poor *general condition seems to be out of proportion to the rather limited in*volvement of the lung

The physical examination reveals diminution of the movement of the right base of the lung Dullness in an area much higher than the usual limits of the liver suggests an increase in the size of this organ if one is aware of this possibility, or may raise the suspicion of an effusion However the typical outline of the effusion is lacking in most cases Auscultation at the right base shows the diminution of normal breathing and even the disappearance of breath sounds when dullness is extensive In many instances pleural effusion is suspected and an exploratory puncture is done As a rule no fluid is withdrawn with the exception of some blood

The roentgenological findings are characteristic and lead in most cases to a definite diagnosis.

The liver is higher, definitely more dense or opaque to the x rays and is immobilized A slight haziness at the right pulmonary base can be discovered making the contour of the right hemidiaphragm slightly foggy In other instances, the right cardiophrenic or costophrenic angle is occupied by a more or less dense shadow

Another finding seen in many cases is a superimposed shadow above that of the liver This shadow is clear cut, crescent shaped, with a diameter smaller than that of the liver silhouette, with uniform density which is much less than the hepatic

When this appearance is discovered the diagnosis of hepato-pul

monary amebiasis is made at once *This roentgenological sign is pathognomonic*

The laboratory findings do or do not confirm the etiology, nevertheless, the appearance of the semilunar shadow as described is decisive in making the diagnosis

It is usual to find a degree of anemia in accordance with the destruction of the liver The decrease in hemoglobin is also remarkable Leucocytes are increased in number although not in the usual proportion found in other suppurative conditions except when another disease complicates the particular case Between 9 000 to 12,000 leucocytes per mm are found in the majority of cases although the expectoration may already seem purulent

As stated before, the examination of the feces may or may not reveal the presence of cysts, without modifying the diagnosis Ochsner has reported a high proportion of cyst findings in sputum but in the experiences of others these are not found in the sputa and in our series we found these cysts only once in the most severe case of the few reported here

Nevertheless we should persist in the search for cysts in order to obtain further confirmation of the diagnosis

In summarizing the syndrome we may state that the main features of this condition can be described as follows

(1) An acute, subacute or chronic, very severe hepatitis with respiratory symptoms Cough without or with expectoration Rather scant purulent sputum or abundant, redish, characteristic in the advanced stages

(2) The clinical and roentgenological findings are located in the right lower lobe in close connection with the diaphragm

(3) The participation of the liver is revealed by inconstant pain in the region, rising of the hepatic cupola, akinesia of the right diaphragm

(4) Roentgenologically the finding of one of three aspects in the initial stage of the lung invasion (a) Haziness of the contour of the diaphragm, (b) triangular shadow occupying the cardio-phrenic angle or the costo-phrenic angle, and (c) crescent shaped, soft, uniform shadow, superimposed on the hepatic cupola The association of this third

aspect with the rising of the diaphragm is in our opinion pathognomonic of the early stage of the amebic lung abscess (1948)

(5) In the early stage disproportion between the moderate changes from the physical and roentgenological standpoints and the severity of the general clinical condition

(6) The absence of a history of dysentery as well as the lack of positive findings in the feces is very common

(7) Cysts are exceptionally found in the sputum

(8) Emetine or chloroquine diphosphate treatment is of definite efficacy and gives evidence of the etiology by a change in the clinical condition immediately In a few days the shadow in the right base disappears and the liver decreases in size and descends to its normal level in most cases

Differential Diagnosis

FROM TUBERCULOSIS

(a) By the characteristic participation of the liver and the roentgen shadow as described (b) Also by the severe clinical picture contrasting with the small x ray changes as revealed in the early stage (c) The absence of tubercle bacilli in a suppurative disease is against tuberculosis

FROM NONAMEBIC ABSCESS

(a) The slight density of the shadow in the characteristic location (b) The scarcity of purulent sputum (c) The definite participation of the liver (d) The moderate increase in the number of leucocytes with a moderate proportion of neutrophiles (e) The rapid and striking action of emetine checking the progress of the disease and changing the clinical aspect in a most dramatic way In the advanced stage differentiation from nonamebic abscess in close connection with the liver should be treated with emetine to rule out amebiasis

FROM PULMONARY INFARCTION

By the pathogenesis of infarction the early bloody sputum the previously good general condition contrasting with a long lasting poor general condition in association with the liver involvement

FROM BASAL PNEUMONIA AND PLEURITIS

The main differentiation is based on the apparent lack of increase in size or elevation of the liver

FROM SUBPHRENIC ABSCESS

The differentiation can be very difficult as both conditions present a similar picture However, the subphrenic abscess not caused by amebas more often tends to provoke pleural effusion This statement is contrary to the one of Anagnostopoulos who mentions the frequency of pleural effusion in epidemic hepato-pulmonary amebiasis Most writers, like ourselves, do not agree with that experience

FROM EMPYEMA

In cases of pathognomonic character, as described, there should be no reason for confusion Other forms, however, can be confused The condition of the liver rules out the diagnosis of simple empyema

Treatment

Very few diseases respond as quickly and dramatically to treatment as amebic dysentery does to emetine treatment

It is a fact that emetine is the example of specific therapy on account of its definite action against the disease Furthermore, response to it when it is immediately demonstrable is usually taken as a confirmatory proof of the diagnosis

In hepato-pulmonary amebiasis the response is rapid and confirmative because no other condition in that location improves in such a striking manner

However the damage already suffered by the hepatic cells may be a handicap for the use of high dosage of emetine as one would tend to employ The toxicity of the drug should make us careful and it is advisable to give moderate doses in two courses allowing an interval so as to avoid cumulative action of emetine

Usually we give a series of 10 intramuscular injections of 0 04 gm (four centigrams) daily and allow an interval of 10 days before giving another course of 10 more injections The total dose is 0 80 gm

The individual dosage varies according to the body weight, from 0 03 to 0 05 gm , this latter dosage being applied to heavier people

The salt used is always emetine hydrochloride and it is of utmost importance to obtain a supply from new stock and of a reliable laboratory, for old solutions are more toxic

After the courses of emetine are finished and in the interval between the two courses we advise 0 30 gm Vioform orally three times a day

for a week Also we give Carbarsone 0 25 gm twice a day for another week or Stovarsol 0 25 gm twice a day for the same length of time

Yatren instead of Vioform may be used (0 25 gm three times a day for a week) with similar results

The improvement, clinically and roentgenologically, is clearly noticeable although the patient may not feel much better because of pains and a depressive feeling which accompanies the use of emetine in many instances

Emetine should be used with caution and its administration should be discontinued when myocardial changes or muscular symptoms of toxic origin appear Close observation of the heart by repeated electrocardiographic tracings is mandatory

Recently, the use of chloroquine (Aralen) has been advocated for the treatment of amebiasis and its complications, including liver abscess The results obtained have been as good and sometimes better than those from the administration of emetine, without the latter's limitations due to its toxicity Chloroquine diphosphate (Aralen) is virtually nontoxic The course of treatment consists of the administration of ten tablets of chloroquine diphosphate (Aralen) of 0 25 Gm each, given in seven days

The first day three tablets are given, the second day two tablets and the third and next days only one tablet until ten tablets are given

This course of ten tablets is repeated after an interval of five days Our experience shows that some cases which fail to show a complete recovery after the use of chloroquine may have further improvement when emetine is given

It is preferable to start the treatment in all cases with chloroquine and give emetine subsequently if necessary

The criteria for the discontinuance of treatment should depend upon the examination of feces until cysts disappear if they had been discovered previously But the clinical appearance, the disappearance of the lung abnormalities, the decrease in the elevation of the liver and of its apparent size should be more important

A long term treatment of the amebic condition is imperative and should be left in the hands of a specialist in tropical diseases

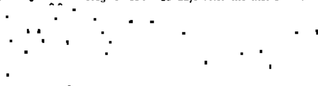


Fig 1 J A Male 31 years Onset three months before with an intestinal infection which left a persistent cough The general cond tion deteriorated until he was seen in consultat on Almost unable to walk Apparent anemia very frequent cough and pink sputum Pulse, 120 Respiration 30 Weight, 54 Kg (Previous weight 80 Kg) No anamnesis revealing dysentery Physical examination only slight rise of the right hem diaphragm Blood count leucocytes 8 900, erythrocytes 3 320 000 hemoglobin 69 per cent eosinophils 3 per cent polymorphonuclears 64 per cent mononuclears 8 per cent lymphocytes 24 per cent

Slight anisocytosis Feces no amoebas or cysts were found Trichomonas and Balantidium coli

The roentgen film shows the pathognomonic aspect Elevation of the d aphragm with the crescent l ke shadow superimposed on the cupola of the liver July 11 1942

Fig 2 J A On Aug 3 1942 23 days after the first film After being treated



Further treatment was advised Yatren Carbarsone

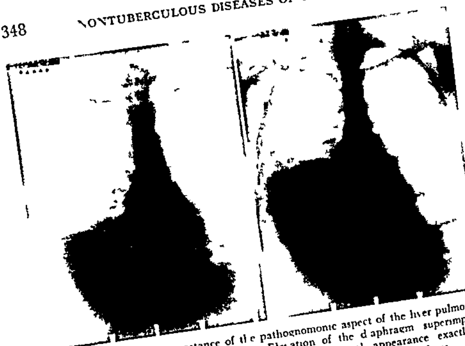


Fig 3 J M Another instance of the pathognomonic aspect of the liver pulmonary complex as seen in the roentgen film Elevation of the diaphragm superimposed crescent like shadow above the hepatic cupola Clinical appearance exactly as described in the text There were cysts of endameba hystolytica in the feces

Fig 4 L C Another type of infiltration which should be suspected of pulmonary amebiasis without being pathognomonic Elevation of the liver with akinesia of the right hemidiaphragm Discrete shadow in the costophrenic angle Very deteriorated general condition compared with the slight changes in the lung



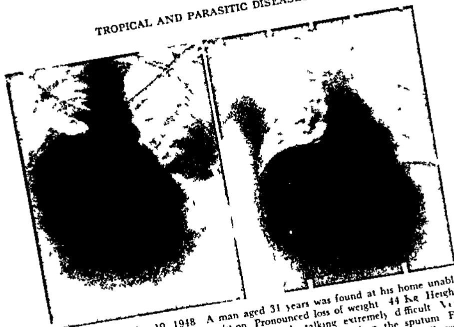


Fig 7 C C May 10 1948 A man aged 31 years was found at his home unable to leave h s bed in a cachet c condit on Pronounced loss of weight 44 Kg Height 6 ft Pulse 130 Intense dyspnoea wh ch made talking extremely d fficult Very frequent cough and muco-purul nt sputum Never had blood in the sputum For over six months he had been treated for tuberculosis although tubercle bacilli wer never found in the sputum

Physical examination revealed very high level of dullness above the lower scapular angle and reaching anteriorly to the clavicle on the right s de On the left s d subclavicular dullness of lesser extent

Auscultation Right s de absent breath sounds over almost the entire right s de However under the clavicle respiratory sounds were accentuated No rales

On the left side auscultation was negative

Sputum examination No tubercle bacilli No oth r m cro-organ sms were found in significant numbers The roentgen film showed extensive shadow on the right s de almost reaching to the right clavicle On the left s de another less extensive shadow was noted with the appearance of an excavation

Fig 8 C C one month later After treatment with emetine total dosage 0 80 gm in 20 days The roentgen film shows defin te improvement The shadows disappeared Only the diapl ragm rema ns in h gh position

←

Fig 5 H L Sl ght changes in the base suggesting pulmonary amebiasis

Sl ght shadow on the cupola of the right hem d aphragm immob lization of the same hem d aphragm General cond tion o it of proportion to these sl ght changes

Fig 6 H L Treatment with emetine made the shadow almost d sappear in two weeks and the general condition improved strikingly This response is also characteristic of hepato-pulmonary amebias s

C C, three years later March 5 1940 The diaphragm remains elevated but less so than in the preceding picture He has gained 36 Kg and has led a normal life ever since Seen in 1945, his condition remained satisfactory However in 1919 as a result of an automobile accident he had a direct trauma on the right subchondral region His general condition deteriorated, persistent fever, marked asthenia and pain on the affected region for longer time than could be expected in a normal person led him to seek medical advice In the X ray film subphrenic collection of fluid and gas was noticed with definite fluid level A course of emetine was given and he recovered very easily in a few days This accident suggests the possibility of latent amebiasis with only an active episode provoked by the trauma to the liver The rapid response to emetine sustains this assumption

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HYDATID DISEASES OF THE LUNG

By GUMERSINDO SAYAGO M D

Hydatid disease of the lung represents the larval stage (hydatid) of Taenia echinococcus In primary echinococcus infection, the egg of this Taenia, eliminated with the dog s feces is taken into the stomach, its envelope is dissolved The embryo (exacanto) so liberated passes through the portal circulation diaphragmatic vessels or a systemic vein and thus reaches the lung

Etiology

The great majority of cases of hydatid disease are reported from Iceland, Australia, the Argentine Republic and Uruguay Thus the principal geographic distribution corresponds to countries where man due to his work, lives in intimate contact with the main sources of infection, namely dogs and cattle In the Argentine Republic, the prevalence of hydatid disease prompted Wernicke to say "I do not believe that there is any Argentinean physician who has never seen a case of hydatid disease '

On the American continent, particularly in Central and North America, cases of hydatid disease are rare and generally, they originate from other countries According to Alonzo in the Argentine, porcine, ovine and bovine cattle are the most infected as found in the following order of slaughtered animals 17 05, 10 25 and 9 62 per cent respectively, as recorded in 1934 From the same country, Greenway and Castex reported 3 095 operated cases of hydatid disease between 1922 and 1935 In Cordoba, Argentina, in our old service of the Instituto de Tisiologia the coexistence of tuberculosis and hydatid disease was found in 2 8 per cent of 569 necropsied individuals who died of tuberculosis between 1939 and 1943 The same incidence was registered at the Anatomical Pathological Service of the Hospital de Clinicas of Cordoba

In Argentina, pulmonary localization of hydatid disease occurs in 14 6 per cent of the cases It is second to the liver in frequency, where it is found in 64 45 per cent of the cases, as determined by Greenway

There is no predisposition to the acquisition of hydatid disease Its development is predicated upon opportunities for contracting the infection through one's occupation, habits, age, place of origin and others



ig 1 Hydatid membrane from an intact cyst uncompl cat d surg cally removed from Piaggio Blanco y Garcia Capurro)

Pathogenesis

The chief localization of hydatid disease in the liver and the lung is readily understood if one considers the life cycle of this parasite When the egg of T echinococcus reaches the stomach of an individual, its envelope is dissolved The embryo (exacanto) so liberated passes through the wall of the stomach or intestine It reaches the portal circulation diaphragmatic vessels or a vein of the greater circulation and thus it reaches the lung This is the manner in which primary echinococcus disease of the lung develops Also echinococcus infection of the lung may be a secondary manifestation of hydatid disease This form may be brought about by metastatic extension from another cyst in the liver, another adjacent organ or the same lung New cysts develop as the result of spread in the lung parenchyma of scolices and vesicles

Morbid Anatomy

Once the hydatid appears in the form of a vesicle which contains a clear transparent hyaline fluid pathologic changes take place in the contiguous lung tissues These changes lead to the formation of a cover or envelope which is designated as adventitious membrane or capsule Thus the parasite itself as well as the lung contribute to the structure of the hydatid cyst Hydatid disease of the lung in its primary form appears generally as a round solitary cyst with well defined borders Its size varies greatly according to the stage of its development from well circumscribed ovoid formations which are scarcely recognizable to that of the head of a foetus Cases in which there is a second cyst on the same side or in the opposite lung are not rare Multiple cysts originate from secondary echinococcus infection as a result of bronchial seeding or hematogenous spread

The adventitious membrane which envelops the hydatid is separated from it only by a potential space With the growth of the cyst bronchi generally small ones, reach this space This relationship persists in the most varied aspects of the disease and is responsible for many of its complications Development of the cyst toward healing by the death of the parasite has been observed in the liver and spleen Also it may rarely occur in the lung Commonly, the cyst has a tendency to rupture into the bronchial lumen This brings about the appearance of hydatid vomica which in a number of instances results in cure without therapeutic measures Rupture of the cyst into the pleural cavity may occur also In such cases the coexistence of a bronchial communication leads to hydropneu



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mothorax Lastly, infection of the cyst with consequent rupture is very frequent Fossati has observed 22 infections in 30 cases

Clinical Study

The first stages of development of hydatid disease are insidious On the basis of clinical experience, in countries with the greatest prevalence of the disease, Escudero asserts with valid reason that of all pulmonary diseases, hydatid disease is the best tolerated by the body It becomes manifest very slowly two years being necessary from the time of implantation of the embryo exacanto to the appearance of the first symptom Accordingly, in the assessment of this disease we must recognize two clinical forms 1) The nonapparent, 2) the apparent The former is represented by cases in which the hydatid cyst is discovered only with the aid of roentgenologic examination When in x ray surveys hydatid disease is incidentally discovered close questioning may reveal symptoms the patient had not mentioned before This is the situation in the case represented in Figure 2 The patient was a pregnant woman registered in the Public Maternity Service where systematic chest x ray examinations are in effect True asymptomatic forms of hydatid disease of the lung generally correspond to recent cysts which due to their incomplete development and their central location do not produce pressure symptoms This represents the most favorable outlook for surgical intervention



Fig 2 Hydatid cyst discovered by radiological survey in a Public Maternity Institute

Apparent forms of hydatid disease include cysts of primary echinococcus infection as well as those with secondary infection produced by another cyst in the same lung or in another adjacent organ Because of limitations of space, we will deal only with primary hydatid cysts The latter can be assayed according to the following classification 1) Closed hydatid cysts, 2) open hydatid cysts, and 3) residual lesions distant from the spontaneous or surgical aperture of the cyst

Closed Hydatid Cysts

These cysts usually contain hyaline material The latter may become purulent as the result of infection which is always a threat Clinical symptoms appear at the time when it becomes possible to visualize the cyst roentgenologically It is possible to correlate the symptoms with the location of the cyst The site of the cyst varies The basal region of the lung is more frequently involved than it apex Tossati found basal localization in 70 7 per cent, with the disease in the right lung in 70 per cent of the cases The cyst may be situated centrally, surrounded by normally ventilated lung parenchyma or peripherally near the pleura With the progress of their growth, central cysts will reach the periphery or an interlobar fissure or the mediastinum Thus, as suggested by Escudero we have to distinguish between primary and secondary peripheral cysts according to their original site of development

Symptoms Dependent upon the Topography of the Cyst

When the cyst is peripheral the overlying pleura is usually affected Consequently, pain is frequently an early symptom The pain is localized in the region of the cyst It is slight in intensity but it is persistent Sudden lancinating pain signifies the rupture of the cyst into the pleural cavity Such an event results in the clinical picture of hydatid pyopneumothorax The pain denotes pleural reaction which sometimes is associated with slight increase in temperature Central cysts which do not reach the pleural surface cause no pain

Physical Signs Dependent upon the Topography of the Cyst

The larger and more superficial is the cyst the more evident the physical signs Respiratory excursions may be reduced over the entire hemithorax or over the zone which corresponds to the site of the cyst Localized bulging of the chest may be found, especially in young persons with large superficial cysts When the latter is at the base of the lung,

palpation reveals absence of vocal fremitus This finding may suggest pleural effusion Dull percussion note is found over large superficial cysts at the base This circumstance enhances the possibility of mistaking hydatid disease for pleural effusion although the superior border of dulness is generally toward the axillary zone The area of dulness over the cyst has a clear demarcation from the adjacent lung parenchyma provided the latter is not affected by some inflammatory process or atelectasis The breath sounds may be found distant or absent depending upon the size and the closeness of the cyst to the surface of the lung Inflammatory changes which frequently occur in the lung parenchyma adjacent to the cyst determine the appearance of adventitious breath sounds Physical signs may strongly suggest the presence of pleural effusion We have often observed basal cysts which were aspirated in the mistaken belief that there was an underlying pleurisy with effusion Fig 3 represents a person who consulted our Dispensary with the presumable diagnosis of pleural effusion The roentgenogram shows besides the circular shadow a displacement of the heart The Casoni test was positive and surgical intervention confirmed the diagnosis It is well to remember that physical signs are insignificant or entirely absent in central cysts and in smaller peripheral cysts

Symptoms not Dependent on the Location of the Cyst

Dyspnea is a symptom that acquires importance with the increase in size of the cyst This symptom, however, is not constant Large cysts without dyspnea are not the exception Letulle considered dyspnea as an early symptom that sometimes may simulate bronchial asthma Pressure symptoms depend upon the topography and the size of the cyst as in the case of tumors, but they are infrequent Cough is an early and very frequent symptom Commonly it is dry and inconstant but when it is associated with expectoration it persists during the whole development of the disease Expectoration is at first mucous It may become mucopurulent or purulent when infection is added to the mechanical irritation of the bronchi Some clinicians say that hemoptysis is rare in this condition but we encountered this symptom in about 50 per cent of our cases Hemoptysis may have a recurrent tendency Sometimes it occurs shortly before the rupture of the cyst Also it may appear simultaneously with or after the rupture of this structure When hemoptysis occurs with the rupture of the cyst, the elimination of the fluid and the membrane of the hydatid cyst may be unnoticed by the

patient In the case represented in Figure 4a copious hemoptysis was simultaneous with the rupture of the cyst its recurrence necessitated artificial pnumothorax for its control After the institution of artificial pneumothorax it was possible to prove the nature of the affection roentgenologically (Fig 4b) It was visualized as an open cyst with fluid and with the retained membrane floating on its surface Hemoptysis after the rupture of the cyst is very serious not only because of its frequency but also on account of its intensity On the other hand hemoptysis with intact cysts is more frequent and less pronounced Hemoptysis simultaneous with the rupture of the cyst although inconstant sometimes may have a fatal termination Early hemoptysis is an incorrect term because hemoptysis appears only when the cyst has already reached significant development



Fig 3 Large hydatid cyst of the right pulmonary base with dislocation of the heart mistaken for pleurisy Operation confirmed the diagnosis

Open Hydatid Cysts



Fig 4a. Shows the image of the cyst previous to artificial pneumothorax with a round shadow, subclavicular on the left with ill defined borders

Fig 4b The same case as of the Figure 4a but after artificial pneumothorax showing the cavity of the ruptured cyst with fluid level and with the hydatid membrane floating partially above the level as *camalote*

The natural development of hydatid cyst is toward its rupture Degenerative processes in the hydatid cyst may lead to its transformation into a solid pap with subsequent calcification as we have observed in two cases in the spleen With the growth of the hydatid, intimate contact takes place with the bronchi and bronchioles adjacent to the parasite The bronchial wall and the adventitious membrane of the cyst atrophy at some site and thus a direct relationship is established between the bronchus and the membrane of the hydatid Consequently, early infec

tion, even suppuration, of the cyst becomes possible prior to its spontaneous rupture With the elimination of some of the hydatid fluid through a fissure in the membrane and the adjacent bronchus, entry of air from the bronchus becomes possible In this manner, a partial separation of the adventitious membrane is produced This is recognized in the roentgenogram as the pneumoperivesicular shadow of Morquio, Bonaba and Soto A check valve type of bronchial obstruction may have an active part in its development as noted later by Bonaba and Soto Fig 5 shows the pneumoperivesicular image in case with artificial pneumothorax The air bubble between the adventitious membrane of the cyst and the hydatid presents the appearance of a cap which occupies the upper external part, holding off the envelope of the hydatid This case was apparently cured without rupture of the cyst, with the embedding of the membrane of the hydatid, but some years later, recurrent pulmonary hemorrhages revealed that recovery had been incomplete



Fig 5 "Pneumoperivesicular image in the form of an air cap separating the adventitious membrane of the cyst of the proper envelope of the hydatid There is artificial pneumothorax

Rupture of the cyst into the bronchial lumen leads to the appearance of one of the most frequent (in one half of the cases) and most important manifestations of hydatid disease, namely the hydatid vomica This confirms the diagnosis Sometimes it represents the first symptom of the existence of the disease Rupture of the cyst may occur without previous hemoptysis On the other hand, cases of operated intact cysts in which their development was accompanied by repeated hemoptysis are not

rare The vomica which follows the rupture of the cyst into the bronchus is associated with attacks of violent cough, dyspnea, respiratory distress and pain The vomica may be limited to the elimination of more or less clear, transparent fluid of the hydatid (hydatoptysis) or turbid, yellowish fluid if the intact cyst was infected In this case, the retained hydatid membrane appears partially floating on the surface of fluid in the vomica The roentgenologic appearance of these changes is known as the sign of "camalote" (a river plant called water lily, resembling a floating island) since its description by Lagos Garcia and Segers of Argentina Although hydatoptysis is sometimes ignored by the patient, generally it represents a dramatic event Violent attacks of cough are associated with the elimination of fractions of the hydatid membrane which are not unlike boiled white of egg, and with the expectoration of daughter cysts resembling grape skin Sometimes, severe pulmonary hemorrhage sets in in this connection In exceptional cases, death occurs during the rupture of a cyst, with the clinical picture of asphyxia, as we have seen it in a man aged 72 years



Fig 6 Planigraphy of the same case of Figures 4a and 4b, which shows the shadow of 'camalote'



Fig 7 Residual hydatid cavity definitely cured by the induction of artificial pneumothorax for a short period

With the total elimination of the hydatid a residual cavity appears On its ultimate development depends the cure of hydatid disease If the adventitious membrane is rigid a frequent occurrence in intact infected cysts the cavity persists and suppuration prolongs the duration of the disease unless appropriate surgical intervention is carried out Sometimes a suppurative residual cavity attains a larger size than that of the cyst from which it originated This is brought about by a bronchial check valve mechanism which leads to intracavitary hypertension by permitting the ingress of air but preventing its egress It may acquire a character which justifies the term hydatid pyopneumocyst suggested by Devet

Residual hydatid cavities may heal spontaneously when the adventitious membrane of the cyst is not rigid and the elasticity of the adjacent pulmonary tissue is preserved as illustrated in Figure 7



Fig 8 Hydatid hydropneumothorax In the sketch we see the details of the film Above the ruptured cyst with its fluid level we find the membrane of the hydatid and the fluid level of the pleural cavity The lung is collapsed



Fig 9 Bronchography reveals bronchiectasis in the left apex where 15 years previously a hydatid cyst healed

The cyst may rupture toward the pleural cavity This is accompanied by intense pain, sometimes urticaria and progressive dyspnea as in the case of check valve pneumothorax Early hydropneumothorax is followed by pyopneumothorax Hydatid membrane may get into the pleural cavity or partially retained at the site of the rupture The rupture of the cyst into the pleural cavity may be associated with simultaneous rupture of the cyst into a bronchus This brings about the coexistence of hydatid vomica and hydatid pneumothorax If the evacuation of the cyst into the pleural cavity had been incomplete, the roentgenogram shows a typical hydropneumothorax as well as the hydati cyst in the adjacent lung tissue In Fig 8, one can see at the base the lung a ruptured cyst with its fluid level and above it, evidence hydropneumothorax in which one can recognize the hydatid membrane

Residual Lesions after the Rupture of the Cyst

We have already referred to residual cavities caused by the rupture of the cyst and considered the influence of the rigid adventitious membrane on its persistence as a result of chronic inflammatory processes which also affect the adjacent lung tissue But in cavities with resilient walls, the decisive factor in their persistence is a check valve type of bronchial communication or the partial or complete persistence of the hydatid membrane enclosed in its interior In such cases, suppuration takes place and the patient dies unless appropriate surgical measure are carried out Sometimes, small residual cavities produce only scant symptoms which are not disturbing at all Only in the late stages, th appearance of hemoptysis calls attention to their existence Then th cavity is discovered on an ordinary roentgenogram or with the aid bronchography Also, in case of pulmonary hemorrhage, bronchograp may reveal bronchiectasis The latter may be the source of persist purulent expectoration An instance of such bronchiectasis is illustrated in Figure 9

Diagnosis

Symptoms and signs of hydatid disease enable us to make a diagnosis in countries where the disease is endemic Visualization of the hydatid vomica confirms the diagnosis, especially when we find rests of the hydatid membrane in the expectorated material and daughter cysts as well as the presence of hydatid hooklets Prior to the rupture of the cyst, the presence of a globular shadow permits good orientation for diagnosis When the characteristic shadow of the cyst is accompanied

by the pneumoperivesicular image of Morquio or by a "camalote" shadow (Fig 6), the diagnosis may be considered certain

Aspiration of the cyst, which permits the demonstration of clear, transparent fluid with sodium chloride and without albumin and eventually hydatid hooklets, confirms the diagnosis Diagnostic aspiration, however is a hazardous intervention, therefore, we cannot recommend its use The following complications may occur after diagnostic aspiration 1) The appearance of hydatid vomica with asphyctic character, 2) serious pulmonary congestion, 3) pulmonary suppuration Eosinophilia when present is another presumptive sign of diagnosis, but its presence is inconstant The complement fixation test is very accurate but it is frequently negative especially in cases of infected cysts The intradermal reaction of Casoni is also inconstant Hydatid fluid is used for this test The reaction presents an early response of the allergic type characterized by edema and redness of the skin at the site of injection and by a late (delayed) response

Treatment

Pneumonotomy for the extirpation of the parasite is practically the only effective treatment of hydatid disease Surgical therapy varies according to given circumstances, that is whether one is dealing with an intact cyst, a suppurated one or with a cyst which already had ruptured In some cases pulmonary resection may be indicated Biological treatment with hydatid fluid, hydatid membrane or scolices, singly or in combination, should not rule out surgical intervention

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CLONORCHIASIS WITH PULMONARY INFILTRATION

By ANDREW L. BANYAI, M D AND J WINTHROP PEABODY, M D

Clonorchiasis is a parasitic disease frequently encountered in China, Korea, Japan and Indo-China It is caused by the Oriental (Chinese) liver fluke, Clonorchis sinensis The adult worm is flat and measures from 10 to 25 mm in length and from 3 to 5 mm in breadth It is found in the bile passages of man, dog and cat Its eggs are ovoid in shape and yellowish-brown in color The eggs measure from 27 to 35 microns in length and from 11 to 19 microns in width They embryonate in the bile passages of the host, from here they reach the intestinal tract and are evacuated Subsequently, the eggs hatch in certain species of snails after ingestion by the latter The cercariae which thus develop in from four to five weeks are discharged by the snail and penetrate into the skin or flesh of certain species of fresh water fishes Here they produce cysts When human beings or other hosts ingest these cysts with raw or poorly cooked fish, the cysts are digested and the parasites (metacercariae) escape in the duodenum and pass through the common bile duct into the bile passages of the liver where they mature into adult worms Consequent inflammatory changes in the liver consist of proliferation and desquamation of the biliary epithelium and of perifocal fibrosis

In persons with mild infestation with this parasite, no symptoms are noted With moderate and severe infestations, one finds gastro-intestinal disturbances, diarrhea, edema, jaundice, hepatomegaly, symptoms of portal cirrhosis, palpitation, weakness, dizziness and tetanic cramps

A case of clonorchiasis with pulmonary infiltration observed in a human being was recorded by Cartwright The salient features of his findings were summarized as follows "This patient (a white male, aged 21) entered the hospital (Shanghai, China) with a complaint of low back pain which was irrelevant to the condition under discussion On admission an eosinophilia of 20 per cent was present He was asymptomatic except for the initial complaint During the hospitalization he developed chills, an intermittent low grade fever and clinical and roentgenological evidence of bilateral pulmonary infiltrations The physical signs were fleeting but the infiltrations were slow in resolving Following detection of the pulmonary lesions, he developed a cough productive of small amounts of sputum containing many eosinophiles, as well as leucocytosis associated with an increase in the eosinophiles in

the peripheral blood to 74 per cent A differential count of the bone marrow following sternal puncture revealed that 46 per cent of the cells were eosinophiles"

Diagnosis is based on the demonstration of the eggs of the parasite in the stool This may require numerous repeated examinations Physical and roentgenologic examinations show pulmonary infiltrations of limited extent The latter is to be differentiated from Loeffler's syndrome and other pulmonary infiltrations due to allergy, also from pulmonary eosinophilosis (tropical eosinophilia), paragonimiasis, schistosomiasis, pulmonary acariasis, sarcoidosis, diseases of the hemopoietic system associated with eosinophilia bronchopneumonia of bacterial, rickettsial, viral or protozoal origin and infestation with animal parasites not mentioned previously

Treatment

Craig and Faust state that intravenously administered sodium antimony tartrate is effective in reducing the number of parasites in the bile passages Also, they endorse the use of medicinal gentian violet (methylrosaniline chloride) in doses of 1 grain (0 06 gm) given orally in enteric coated tablets three times a day before meals for one month Also, chloroquine (7-chloro-4-[4 diethylamino-1-methylbutylamino] quinoline) is of curative value For adults, it is prescribed in the form of tablets of 0 25 gm four times a day for three days, followed by two tablets a day for three weeks Cartwright (1949), without claiming specificity for the arsenicals, used mapharsen successfully in his patient with pulmonary infiltrations He gave six intravenous injections of this drug, with a total amount of 0 31 gm , over a 16 day period

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CYATHOSTOMIASIS (SYNGAMOSIS)

By ANDREW L BANYAI, M D AND J WINTHROP PEABODY, M D

Cyathostoma (Syngamus Laryngeus) is a nematode which occurs as a parasite of the upper respiratory tract in fowl and in cattle, goats and water buffaloes in the West Indies, South America and the Philippine Islands The descriptive term syngamus refers to the fact that the male parasite which is much smaller than the female, is attached to the latter in permanent copulation Leiper in 1913 first reported recovery of this worm from the sputum of a woman living in St Lucia, West Indies St John and his associates recorded a case of pulmonary infestation with this parasite in a 33 year old man residing in the Philippine Islands The female cyathostoma expectorated by this patient was bright red in color, measured 16 6 mm in length, its diameter at the head about 1 mm and at the posterior extremity 0 66 mm The head was bulbous, with a heavy chitinous wall divided into six equal parts by longitudinal lines Its ova found in the sputum measured 60 by 102 microns, they were oval in appearance and were flattened on one side of their length The ova of cyathostoma are covered with a shell of 2 microns in width with faint transverse striations They contain an eight cell morula According to Craig and Faust, the following sporadic cases of human infestation with cyathostoma have been reported

Author	Date	Geographic Location	No of Cases
Leiper	*1913*	*St Lucia West India*	1
Travasses	1921	Brazil	1
St John *et al*	1929	Philippine Islands	1
Hoffman	1931 1932	Trinidad and Puerto Rico	3
Lent and Pena	1939	Brazil	1

Symptoms observed by St John and his associates were

(1) Prolonged attacks of coughing, usually in the morning on arising, which was relieved by vomiting or by raising tenacious, rust colored sputum

(2) Nightly asthmatic attacks

(3) Persistent, frequent asthmatoid wheeze

(4) Expectoration of bright red blood two months after the onset of the disease

(5) Constant throat irritation

(6) Dull aching pain in the chest

(7) Substernal constriction

Following the expectoration of a single worm, the patient made a rapid recovery

Diagnosis of cyathostomiasis is based on finding the ova or parasites in the patient's sputum

No specific treatment is known Prophylaxis consists of avoiding uncooked food and unfiltered water in regions where this condition occurs

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STRONGYLOIDOSIS

(Strongyloidiasis, Strongyloides stercoralis *infection*)

By Andrew L Banyai, M D and J Winthrop Peabody, M D

Strongyloides stercoralis is an intestinal parasite commonly encountered in tropical and subtropical regions, also, *occasionally in the* southern parts of the United States Patients with intestinal infestation *with* Strongyloides complain of abdominal pain, diarrhea and digestive disturbances Diarrhea may alternate with constipation Mucus is found in the stools, and on rare occasions blood may be noted In mild cases of strongyloidosis, symptoms referable to the gastro intestinal tract may be entirely absent The lung is an important site on the developmental *phases of this helminth Larvae passed with the feces of an individual* suffering with this condition are 200 to 250 microns in length In warm, moist soil, they either develop into adult worms which copulate, the females deposit eggs, with a subsequent development of larvae and repetition of their life cycle or they transform into filariform larvae in 24 hours, which, in turn, penetrate the skin of bare footed exposed persons Once lodged in the human body, the larvae reach the lung through the blood stream and break through into the alveoli Here the larvae develop into adult males and females Following fertilization, the females migrate through the trachea, pharynx and esophagus to the duodenum and the upper jejunum and deposit their eggs into the mucosa about two weeks after the first penetration of the skin by the larvae Occasionally the gravid females deposit their eggs in the mucosa of the lung from which larvae arise thus causing the development of pulmonary strongyloidosis

The pulmonary involvement consists of acute, transitory bronchopneumonia associated with leucocytosis and marked eosinophilia or of *chronic bronchitis and bronchopneumonia which may persist for years* The patient complains of cough, expectoration and occasionally of thoracic pain, dyspnea and *pulmonary hemorrhage These symptoms* are accompanied by headache, anorexia, low grade fever and malaise

Physical and roentgenologic examinations reveal *corresponding find*ings over the lungs The diagnosis is confirmed by the demonstration of the motile larvae of Strongyloides stercoralis in the sputum and the stools

A study of 100 cases was reported by Jones, with a review of the literature Larvae of the parasite were found in 27 per cent of 952 stool examinations, in 20 patients larvae were not demonstrated in the

stools Examination of the aspirated duodenal fluid, however, gave positive results Eosinophilia was the most characteristic feature of the blood picture

The treatment consists of the intravenous administration of 20 cc of a 0 5 per cent filtered aqueous solution of gentian violet on five alternate days Gentian violet is a mixture of pentamethylenepararosaniline and hexamethylenepararosaline hydrochlorides

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CREEPING ERUPTION (CUTANEOUS HELMINTHIASIS WITH ASSOCIATED PULMONARY INVOLVEMENT)

By Andrew L Banyai, M D and J Winthrop Peabody, M D

One of the nematodes, Ancylostoma brasiliense, hookworm of dogs and cats, was first proved to be the cause of creeping eruption (cutaneous helminthiasis) by Kirby Smith and his associates in 1926 Viable larvae of this parasite deposited in warm, moist soil are capable of penetrating the unbroken human skin In a few hours, linear serpiginous elevated burrows appear in the skin The eruptions are associated with intense itching and show a tendency to extension for several weeks

Wright and Gold in 1946 first observed the occurrence of pulmonary involvement in patients with this condition The incidence was 50 per cent They are inclined to believe that pathologic changes in the lung are brought about either by larvae which reach the lung and die there or by the lung serving as a shock organ to the allergens produced by the larvae which remain in their subepidermal location throughout the disease Their observations can be summarized in the following points Roentgenologically demonstrable lung changes are patchy, fleeting and migratory in character They usually become detectable after the seventh day of the cutaneous lesion but in some instances, two months may elapse before their appearance on the roentgenogram The x ray opacities vary in size from solitary, irregular areas measuring 2 by 3 cm to widespread patchy infiltrations in about 75 per cent of the lung fields

Constitutional symptoms are absent in spite of the extensive pulmonary changes Fever is present only in patients with secondary cellulitis Mild, usually unproductive cough was noted in one third of the cases Physical findings over the chest were absent or insignificant in comparison with x ray findings

Wright and Gold found eosinophilia of the peripheral blood which in some cases, reached as high as 51 per cent The eosinophilia was proportionate to the extent of pulmonary changes but persisted for four to six weeks after their complete disappearance Eosinophilic leucocytes in the sputum ranged from 0 to 90 per cent, and remained at such levels parallel to the height and duration of eosinophilia in the blood No ova of Ancylostoma brasiliense, nor the parasite itself was found in the stools on competent examinations Positive intracutaneous tests were obtained with aqueous extracts of Ascaris lumbricoides and Trichinella spiralis in 75 per cent of their patients

Roentgenologic and laboratory findings and the absence of constitutional symptoms qualify this condition as one belonging in the category of Loeffler's syndrome Even so, for the sake of efficient treatment, it is mandatory to differentiate it from other members of this group For respective details, the reader is referred to the chapter on Loeffler's Syndrome Moreover, the following conditions should be taken into consideration

(1) Bronchopneumonia caused by various bacterial and viral agents

(2) Other parasitic infestations with pulmonary involvement

(3) Sarcoidosis

(4) Lymphomatoid diseases

(5) Eosinophilic leucocytosis

(6) Tropical eosinophilia (Pulmonary eosinophilosis)

(7) Diseases which cast widespread nodular shadows in the roentgenogram The list of these is given in the chapter on *Pulmonary Manifestations of Lupus Erythematosus*

Treatment

According to Wright and Gold (1946) roentgenologic pulmonary findings promptly disappear following treatment of the skin lesion They recommend the application of ethyl chloride spray for 30 seconds daily over an area 4 to 5 cm in diameter about the ends of the burrows or tunnels

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and evidence of marked microcytic anemia The only conclusive proof of the disease is the identification of eggs in the stools, larvae in the sputum and rarely, adult worms in the feces

Treatment should be focused on specific anthelmintics, correction of econdary anemia and adequate diet Respiratory symptoms are corected according to the individual requirements of the case Tetrahlorethylene is the specific drug of choice It is given for adults in 3 or cc doses in water, milk or capsules either with or followed by saline urgation It affects the worms in the intestinal tract directly as it passes rough the bowels Two treatments with tetrachlorethylene are considered equivalent to a single dose of carbon tetrachloride The former has a much greater safety than the latter in that it is not likely to cause toxic symptoms through liver damage Its own contraindications are alcoholism and ascariasis In the presence of the latter the administration of hexylresorcinol is called for The dose of hexylresorcinol for adults is 15 grains (1 gm) taken in the morning on an empty stomach and followed by a four to five hour fast It should be administered in capsules each of which contains 0 5 gm of the drug The dosage for children is 0 2 cc for each year of age up to 15 years

According to Faust it eliminates from 75 to 85 per cent of the hookworms

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HOOKWORM DISEASE OF THE LUNG

By ANDREW L BANYAI, M D AND J WINTHROP PEABODY, M D

Hookworm disease (uncinariasis, ankylostomiasis) is prevalent in tropical and subtropical countries Occasionally, it is encountered in countries of temperate climate where the atmosphere is warm and moist and individuals walking about in their bare feet are exposed to contaminated soil The disease is caused by two species of the parasite, namely the Uncinaria americana or Necator americanus (in the United States southern Asia and Polynesia) and by the Ankylostoma duodenale (in Europe, northern Africa and northern Asia) The eggs of these worms are of oval shape, have a smooth surface and contain embryos in various phases of development When the eggs are deposited in the feces on warm, moist soil in a shady location, infective filariform larvae develop in nine days These are capable of penetrating unprotected human skin (usually the feet) and, through the lymph passages and blood vessels they reach the lung where they are deposited After penetrating through the alveolar wall, they migrate through the respiratory tract to the larynx and from here they pass to the esophagus and stomach and settle down in the middle third of the small intestine Here, the larvae develop into mature worms in four to seven weeks The worms are firmly attached to the intestinal wall and withdraw blood from the capillary bed The male worm measures 8 to 10 mm in length and the female 10 to 18 mm Each female lays a few thousand eggs a day, thus giving rise to the renewal of the life cycle Rarely the larvae are ingested with contaminated food or water If this is the case the larvae penetrate the intestinal mucosa and are carried to the lung Here, they go through the usual process of maturation and then return to the small intestine through the esophagus

Pulmonary disease may develop as the result of infestation with hookworm The pulmonary lesion, as revealed by physical and x ray examination, consists of bronchitis or bronchopneumonia The latter is likely to be transient in character General low grade toxic symptoms such as fever, malaise anorexia and headache are noted, together with cough and expectoration The diagnosis is based on a suggestive history which includes anorexia indigestion, eructation epigastric pain alternating diarrhea and constipation, headache, vertigo, unexplained chronic fatigue, emaciation, edema, palpitation, dyspnea and paresthesias Laboratory examination may show leucocytosis, eosinophilia

rhagic expectoration Larvae of Ascaris were found in large number in his sputum for five to 10 days Mueller, Weber, Wild and Loertscher consider Ascaris an important cause of Loeffler's syndrome Cutaneous tests with Ascarides extract were found positive by Zweifel in a higher percentage of patients with transitory eosinophilic pulmonary infiltrations than in the controls In addition to cough, these patients may complain of expectoration, pulmonary hemorrhage and fatigue Possibly slight fever and other toxic symptoms are noted

Physical findings over the chest are usually slight With the exception of lobar involvement, changes in the percussion note and breath sounds may be entirely absent or only a few fine moist rales signify the site of pulmonary disease Diagnosis is suggested by leucocytosis with a high eosinophil count in the blood which may reach 30 per cent Corroborative evidence is the demonstration of ascaris or its ova in the stools or larval worms in the sputum

From the viewpoint of differential diagnosis the same items should be taken into consideration as presented in the chapter on Loeffler's Syndrome

Treatment consists of the administration of hexylresorcinol, a crystalline substance, given in hard gelatine capsules on an empty stomach in the morning No food is allowed after its administration for five hours Saline purgative is given the next morning The dose for an adult and for children over 12 years of age, is 15 grains (1 gm), for children of six to 12 years of age, 10 to 13 grains (0 6 to 0 8 gm) and for very young children, 6 grains (0 4 gm) Its use is preferable to that of santonin or oil of chenopodium because in addition to its high efficiency, its toxicity is much less than that of either of these two drugs Etteldorf and Crawford observed good results with the use of 1-diethylcarbamyl-4-methyl piperazine dihydrogen citrate (Hetrazan, Lederle) They consider it superior to other anthelmintics It is effective without subjecting the patient to fasting or purgation Its dose is 6 mg per Kg of body weight three times a day for at least one week Occasionally 10 mg per Kg three times a day may be required for satisfactory results

Hetrazan syrup was successfully used in 125 children as reported by Hoekinga, but is not recommended for mass treatment because of the multiple doses required Hetrazan in tablet form was successfully used in 20 patients by Loughlin and his co-workers but the syrup is preferable in most instances

ASCARIASIS

By Andrew L Banyai, M D and J Winthrop Peabody, M D

Ascariasis, infestation with the intestinal parasite Ascaris lumbricoides, is prevalent in widespread parts of the world, including countries in the temperate zone Infestation with this helminth is most frequent in children under 10 years of age The female lays about 100,000 eggs daily When these are deposited in moist soil, a process of larval development begins which is completed only with the ingestion of the eggs in contaminated food or water after further hatching in the human intestine The larvae penetrate through the intestinal mucosa and migrate through lymphatics (thoracic duct) and the blood stream (portal and hepatic veins) to the lung From the pulmonary capillaries they reach the open respiratory tract and arrive from the bronchioles to the larynx and pharynx and after a passage through the esophagus and stomach, to the small intestine Here the larvae develop into mature male and female ascarids which measure 20 to 25 cm and 30 to 40 cm in length respectively The fertilization of the latter leads to the repetition of the life cycle

Symptoms referable to the gastro intestinal tract are rather meager Occasionally, loss of appetite or vomiting may occur In rare instances the helminths may cause severe symptoms by migration into the common bile duct or the appendix or cause intestinal obstruction Two types of pulmonary disease may occur as a complication of ascariasis One is bronchopneumonia which results from the migration of adult ascarids into the lung This is a very unusual occurrence It is more likely that pulmonary changes are caused by the sojourn of the larvae in the lung tissue during the process of their developmental cycle In these instances the pulmonary lesion has an insidious onset and is characterized by roentgenologically demonstrable transitory, migratory infiltrations The latter may be unilateral or bilateral, circular or irregular in shape sharply circumscribed or with indistinct borders, varying in size from one to several centimeters Occasionally, the entire extent of one lobe is involved The pulmonary infiltration lasts from three days to a few weeks The lesion consists of inflammatory changes, with local edema of the lung tissue There is localized conglomeration of eosinophilic leucocytes in the alveoli and in the interstitial tissue Koino in 1922, following experimental swallowing of 2,000 ripe, fertilized ova of Ascaris lumbricoides, developed eosinophilic pneumonia with high fever and hemor

TRICHINOSIS

By Andrew L Banyai, M D and J Winthrop Peabody M D

The protean man [illegible]

systemic [illegible]

it is of im[illegible]

acterized [illegible] symptoms and findings When liv[illegible] encapsulated larvae of the Trichinella spiralis are ingested with raw or poorly cooked pork (sausage, hamburgers, frankfurters, meat loaf), the larvae are liberated in the stomach, pass into the intestine, where they mature and copulate The female parasite deposits its larvae beneath the intestinal mucosa, from there they pass through the lymphatics and thoracic duct to the heart and lungs and finally to the voluntary muscles Abdominal symptoms, such as nausea, vomiting, diarrhea, cramps and pain may be slight or absent The systemic dissemination of the larvae takes place during the second week with symptoms such as chills, remittent or intermittent fever, profuse sweating, malaise, headache, muscle pains, muscular tenderness [illegible] of the face, with or without evidence [illegible] us or [illegible] The [illegible] weeks Encystment of the larvae in [illegible] coincides with convalescence and recovery

Respiratory symptoms and findings occur in from 11 to 50 per cent of the cases and are caused either by involvement of the diaphragm, intercostal muscles and of the pleura or by parenchymal disease of the lung Post mortem examination of the diaphragm in unselected cases in various cities of the United States revealed according to Evans in 1938 the presence of encysted larvae of T spiralis in from 5 to 50 per cent As a corollary, it is interesting to refer to the report of Dickman He examined samples of pork sausage and pork chops obtained at random in the markets of one of the metropolitan centers of this country and found that approximately 9 5 per cent of the sausage and 1 5 per cent of the chops contained T spiralis Infestation of the diaphragm may cause pain associated with respiration, particularly with deep respiration Through the phrenic nerve the pain may be referred to the neck and shoulder girdle, and through the six lower intercostal nerves it may be transmitted to the abdomen Partly because of painful respiration and partly due to pulmonary congestion or parenchymal inflammation, the patient may complain of dyspnea Bronchopneumonic, and pneu-

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lowing points are of cardinal importance from the diagnostic standpoint

(1) History of eating uncooked pork

(2) Normal or elevated white blood cell count with a rapidly rising, transient eosinophilia, varying from 6 to 70 per cent The latter usually begins during the second or third week of the illness Absence of eosinophilia does not rule out trichinosis

(3) Detection of larvae by biopsy from one of the voluntary muscles (pectoralis major, trapezius, deltoid, gastrocnemius)

(4) Positive, immediate Bachman test, demonstrable from the second or third week of illness The test is given intracutaneously with 0 1 cc of a 1 10,000 dilution of extract of *T spiralis* larvae in isotonic solution of sodium chloride The positive reaction appears in 20 to 30 minutes and consists of an elevated, edematous central wheal, 8 to 15 *mm* in diameter, with or without pseudopods, and surrounded by an erythematous area which measures from 20 to 50 mm The Bachman test has a high degree of accuracy, but it must be interpreted with caution for the reason that individuals who become sensitized by infestation with *T spiralis* are bound to show a positive skin reaction for years

(5) Rarely, larvae may be found in the sputum, blood and spinal fluid

(6) Positive precipitin test is obtainable from approximately twentieth to the thirtieth day of infestation

(7) Positive complement fixation test

In the differential diagnosis, one should rule out bronchopneumon and pneumonia of bacterial, rickettsial, viral or other parasitic origin Also, transitory pulmonary infiltrations of other etiology, which are associated with eosinophilia, should be excluded A list of these is given in the chapter on Loeffler's Syndrome

Prognosis

Pulmonary disease caused by *T spiralis* runs a self limited course The latter may be aggravated by superimposed secondary infection which, if not treated adequately, may lead to fatal termination

The treatment consists of general supportive and symptomatic measures Cortisone and ACTH have been used successfully by a number of clinicians Diminution of symptoms has been accompanied with loss of fever and temporary fall of circulating eosinophils Favorable alteration of the course of trichinosis has been observed

monic consolidation has been observed from the third to the fifth week. During the course of pulmonary involvement, the fever is moderate or high, the patient has a persistent cough and mucopurulent expectoration. Hemorrhage from the lung is observed in case of pulmonary infarction. The parenchymal lesions have a tendency to clear rapidly. Auscultation may reveal the presence of moist rales and pleural friction sound. Pleurisy with serous, blood tinged effusion, unilateral or bilateral may complicate the condition. The eosinophiles may reach 85 per cent. The pleuropulmonary changes are accompanied by slight or moderate *chilliness, weakness and night sweats*.

Loeffler and his associates produced pulmonary lesions in guinea pigs fed with a small number of larvae of T. spiralis. The animals developed cough between the third and eleventh day subsequently. Roent*genograms of the lung revealed transitory infiltrations. Simultaneously* eosinophilia up to 22.5 per cent (normal eosinophil count is 4 per cent) was recorded. It disappeared within 10 to 14 days. Post mortem exami*nations showed the following pertinent findings*:

(1) Pneumonia and bronchopneumonia which consisted predominantly of infiltration with eosinophilic leucocytes.

(2) Larvae of T. spiralis were demonstrable in the areas of eosinophilic infiltration.

(3) *Serial examinations of animals killed at intervals illustrated* the evanescent nature of pneumonic and bronchopneumonic *infiltrations*.

(4) Areas of sharply demarcated atelectasis were seen either as foci surrounded by pneumonic infiltrations or independently of them. Atelectasis resulted from the occlusion of smaller bronchi by plugs con*sisting of eosinophilic leucocytes* and larvae.

(5) There was evidence of eosinophilic bronchitis and peribronchitis.

(6) Infiltration of the media of the blood vessels with eosinophils was noted in areas of parenchymal infiltration.

(7) Increased eosinophilic myelopoiesis was observed in the bone marrow. The spleen contained a large number of eosinophilic leucocytes with occasional foci of infiltration with the same cells.

The diagnosis of pleuropulmonary trichinosis *should not be difficult even in the absence* of typical manifestations, such as edema of the face, eyelids and conjunctiva, with ecchymosis at the insertion of the ocular muscles, pain and tenderness in the muscles, and joint pain. *The fol*

lowing points are of cardinal importance from the diagnostic standpoint

(1) History of eating uncooked pork

(2) Normal or elevated white blood cell count with a rapidly rising, transient eosinophilia, varying from 6 to 70 per cent The latter usually begins during the second or third week of the illness Absence of eosinophilia does not rule out trichinosis

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TOXOPLASMOSIS OF THE LUNG

By ANDREW L BANYAI M D AND J WINTHROP PEABODY M D

Human toxoplasmosis is caused by a protozoon Toxoplasma which was first identified in North African rodents by Nicolle and Manceaux in 1908 and in Brazilian rabbits by Splendore in 1908 It is a crescentic, pyriform or ovoid parasite which measures from 2 to 6 microns in length and from 1 5 to 3 microns in width Its large nucleus occupies its entire width and is situated near the more pointed end On histologic examination Toxoplasma is found singly within cells or free also it may be seen in the form of globular aggregations designated as pseudocysts Its *natural hosts are dogs pigeons rabbits voles, squirrels and other* rodents It is pathogenic for guinea pigs, mice, chicks and chickens

Cases of human toxoplasmosis have been reported from Europe, the United States and South America In spite of the very limited number of instances recorded it is reasonable to assume a higher incidence of the disease than hitherto recognized It is known that infection with Toxoplasma exists in animals without manifest disease Also it has been shown by Sabin that immunizing specific antibodies are present in the blood serum of persons in apparently good health This is suggestive of a foregone subclinical infection or perhaps a previously unidentified disease caused by Toxoplasma It has been shown that pregnant women may transmit the disease to their offspring without themselves being affected by it

Two forms of toxoplasmosis are recognized

(1) The one seen in infants and children

(2) Toxoplasmosis of adults

The first type is seen as encephalomyelitis with nonsuppurative granulomatous involvement of the central nervous system Chorioretinitis is a usual component of the pathologic findings Multiple calcifications in the brain and hydrocephalus are characteristic of the clinical picture Cerebral calcifications of this type in newborn infants are suggestive of intrauterine infection from a latent toxoplasmosis of the mother Pulmonary lesions are infrequent in association with the childhood form of the disease

The most important manifestation of adult type of toxoplasmosis is interstitial pneumonitis In addition inflammatory changes occur in other organs but their clinical significance is irrelevant Toxoplasmosis in adults was first reported by Pinkerton and Weinman (1940) Pinker

ton and Henderson recorded two other cases in 1941 In one of these, post mortem examination showed that the lung was markedly congested, with hemorrhagic frothy fluid removable from the cut surface There were firm shot like areas of induration, measuring from 1 to 4 mm throughout all lobes In the other case the lungs were solid and edematous, the cut surface grayish white Microscopically, the following findings were noted "The lungs showed a remarkable picture of interstitial pneumonitis, with interstitial organization in many areas Practically every alveolus appeared to be lined with cuboidal epithelium The alveoli contained a gelatinous appearing exudate in which very few inflammatory cells were present, the alveolar walls were often lined with a thick hyaline membrane similar to that seen in influenzal pneumonia Occasional alveolar lining cells, as well as macrophages lying free in the alveoli and bronchioles were distended with toxaplasma "

Prodromal symptoms of the disease, such as weakness, malaise anorexia and diarrhea may last from a few days to three weeks These are followed by headache, chills, fever and simultaneous cutaneous rash Arthralgia and myalgia may be present On close questioning the patient may relate removal of ticks from the body prior to the onset of the illness Fever may reach 104° F (40 0° C) or higher, with remissions of one or two degrees in the morning Relative bradycardia is present The febrile period lasts from six to 16 days Maculopapular rash covers the entire body, with the exception of the scalp palms and soles of the feet The eruptions are of bright red to pale pink in color and measure from 2 to 6 mm Gradual fading of the rash takes place within a week The patient is evidently gravely ill and shows signs of apathy, prostration and with the progression of the disease, increasing cough, dyspnea and cyanosis

Physical examination of the chest reveals nothing characteristic Depending upon the stage of the disease, signs of pulmonary infiltration or extensive consolidation may be noted *Roentgenologic findings in the* two cases of Pinkerton and Henderson were described by Sante (1942) In the early stage of the disease, the appearance of the roentgenogram resembles that of acute pulmonary edema, with diffuse, ground glass opacity and blotchy areas over both lung fields, enlargement of the hilar shadows, increase in the size and number of visible bronchovascular markings At a more advanced stage, there are signs of increasing interstitial infiltration and alveolar exudation, with conglomerate shadows

indicative of irregular patchy consolidation The lower lobes are more involved than the balance of the lung

Laboratory studies are indispensible for establishing the diagnosis These include the following

(1) Detection of antibodies in the blood serum As mentioned before, there are persons whose blood contains immunizing antibodies without any pathologic manifestations Absence of antibodies from the blood serum does not rule out toxoplasmosis The cytoplasma modifying antibody is demonstrable by the methylene blue test of Sabin and Feldman This antibody develops within 10 to 20 days in titers of 1 256 to 1 4,000 The complement-fixing antibody appears later

(2) Examination of the sputum for toxoplasma by simple smear and by inoculation into guinea pig and mice

(3) Animal inoculation with the patient's blood serum Intraperitoneal injection with material which contains Toxoplasma produces nodular necrotic changes in the liver and spleen and hemorrhagic consolidation in the lung Microscopic examination of scrapings from these areas reveals the presence of Toxoplasma Giemsa stain is recommended for staining the slides Syverton and Slavin reported a case in an adult for whom the diagnosis was established by finding Toxoplasma in biopsy specimens taken from the gastrocnemius muscle The micro-organism was identified in histologic preparations as well as by its transmission to guinea pigs, rabbits and mice

Hematologic examination shows a white blood cell count varying from 5,000 to 18,000 per cubic millimeter The differential count is normal, except a slight increase in the number of stab formed neutrophilic leucocytes Syverton and Slavin (1946) recorded eosinophilia in their patient which ranged from 26 to 45 per cent

Urine analysis may show slight albuminuria, with hyalin casts, white and red blood cells in the sediment

In one of the proved cases of toxoplasmosis, positive Weil-Felix reaction was found

Differential Diagnosis

According to Sante, x-ray findings in the early stage of toxoplasmosis should be differentiated from those caused by aspirated liquids, such as water, in drowning, but these changes rapidly disappear Also, one would rule out pulmonary changes caused by aspiration of kerosene and other noxious substances, also pulmonary edema due to waterlogging by

excessive administration of fluids Advanced stages of the disease are to be differentiated from typhus, Tsutsugamushi fever, relapsing fever Rocky Mountain spotted fever, tularemia, typhoid and paratyphoid fever, brucellosis, trichinosis, acute interstitial pneumonitis, pulmonary adenomatosis, atypical (virus) pneumonia, fungus infection of the lung severe pulmonary edema and inflammatory parenchymal changes of the lung caused by various other pathogenic micro organisms

The prognosis of toxoplasmosis in adults is grave Recovery occurred in the case of a 65 year old white man 20 days after admission to the hospital, as reported by Syverton and Slavin (1946)

Treatment

Weinman and Berne found that sulfapyridine successfully cured toxoplasmosis in experimental animals Also, they noted that latent infection remained after recovery Sulfadiazine and sulfamerazine are also effective Robinson (1947) treated a child with the meningo-encephalitic form of the disease Recovery was attributed to the combined administration of sulfathiazole and emetine Penicillin, streptomycin aureomycin and other antibiotics are without any effect

Supportive and symptomatic measures are mandatory, including the use of oxygen by inhalation for the relief of dyspnea An elderly woman with toxoplasmosis in spite of treatment with aureomycin, penicillin streptomycin sulfadiazine corticotropin and chloroquine, reported by Kass *et al* died but at post mortem showed apparent healing of many lesions and such therapy is suggested in mild cases with hope of cure

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ACARIASIS OF THE LUNG

By Andrew L Banyai, M D and J Winthrop Peabody, M D

Respiratory complaints attributable to infestation with tyroglyphus and trasonemus mites were first reported from Southeast Asia by Carter and his associates in 1944 Symptoms were noted after exposure to dust of stored rice and other cereals, flour, sugar, tea, coffee, dehydrated vegetables, spices and emanations from cheese, dried fish, linen and leather goods

Onset of the disease is insidious with mild, intermittent unproductive cough suggestive of bronchitis The cough is worse at night and is associated with expiratory dyspnea and wheezing Subsequently, typical asthmatic attack develop with gradually increasing frequency The attacks are more common at night Consequently, the patient complains of loss of sleep, lassitude and malaise on arising There is a slow deterioration of general physical well being Cough becomes productive of tenacious, mucopurulent sputum The latter is occasionally blood tinged

On physical examination sonorous and sibilant rales are heard throughout both lungs and occasional fine moist rales over limited areas

Roentgenograms of the chest reveal a ground glass appearance of the lung fields, enlarged hilar lymph nodes, fine nodular opacities widely distributed in both lungs, or transitory, patchy bronchopneumonia like shadows near the hilum or at the periphery The latter changes may be of allergic origin not unlike other well known manifestations of Loeffler's syndrome The disseminated small mottlings correspond to pathologic alterations produced by Davis experimentally in a Macacus monkey On necropsy of this animal, he found small nodules throughout both lungs The nodules were in the vicinity of, but not in direct contact with bronchioles Mites were detected within these nodules Microscopic examination showed that the wall of each nodule consisted of cellular granulation tissue, with fibroblasts, leucocytes, plasma cells and endothelial cells The inner aspect of it was lined with epithelial cells The nodules usually contained a mite lying in cellular debris

Laboratory examinations are indispensable in the diagnosis Thorough search for mites reveals their presence in the sputum either in the hypopal stage or in adult form The number of white blood cells varies from 10,000 to 37,000 per cubic millimeter A striking, constant finding is eosinophilia in the peripheral blood, which may be as high as 80 per cent

In the differential diagnosis, due thought should be given to ruling out the following conditions

1 Bronchitis and bronchopneumonia caused by bacterial or viral agents

2 Bronchial asthma due to other causes

3 Tropical eosinophilia of undetermined origin (Pumonary eosinophilosis)

4 Sarcoidosis

5 Infestation with other animal parasites

6 Loeffler s syndrome due to nonparasitic allergens

7 Cave sickness

8 Diseases which cast widespread nodular shadows on the roentgenogram These are described in the chapter on Collagen Diseases of the Lung

Treatment

Excellent results have been observed from the use of arsenicals Neoarsephenamine is given intravenously in increasing doses of 0 15 to 0 3, 0 45 and 0 6 Gm at four day intervals Also, recovery follows the oral administration of acetarsone, carbarsone or stovarsol in doses of 0 25 Gm twice daily for 10 days

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CHAPTER VIII

TUMORS

BENIGN TUMORS OF THE BRONCHUS

By Louis H Clerf, M D

Benign tumors of the tracheobronchial tree although uncommon probably are not as rare as medical literature would indicate Comparative studies of the occurrence of primary benign and malignant bronchogenic tumors suggest that two to four per cent of all tumors are benign Adenoma is the most common but cases of papilloma and tumors arising from the various connective tissues and vascular structures have been observed Polyps and other inflammatory tumor like growths also are encountered particularly in cases of bronchial foreign body of long sojourn, pulmonary suppuration and tuberculous tracheobronchitis and are equally as important as primary benign tumors because of the production of bronchial obstruction with its complications

Symptoms

Benign bronchial tumors are slow growing and the occurrence of symptoms therefore is insidious There may be an absence of symptoms until a superimposed bronchopulmonary infection or bronchial obstruction supervenes The symptoms commonly depend upon the location of the growth, the degree of obstruction, the presence of inflammatory changes and interference with drainage An important early symptom which often is overlooked is wheezing respiration This occurs during the period of partial bronchial obstruction and is best heard at the open mouth during and particularly towards the end of forced expiration The presence of a tumor in the bronchus often induces an irritative cough and frequently there is an increase in mucoid expectoration Hemoptysis is a common and often a first symptom With increasing obstruction of the bronchus by the tumor and retention of secretions there often are periods of chilliness, slight fever, and an increase in cough and quantity of sputum When the obstruction becomes

complete, atelectasis of the lung occurs with retention of secretions, infection, drowned lung, fever and at times hemoptysis, ultimately the symptoms of chronic pulmonary suppuration supervene Pain is uncommon as an early symptom Its occurrence is usually associated with suppuration and involvement of the pleura

Physical Signs

The physical signs are those characteristic of bronchial obstruction In the early stages when the obstruction is slight and there is wheezing respiration the wheezing may be heard over the involved lung There may be diminution of breath sounds beyond the point of stenosis With increasing obstruction the physical signs become more prominent If the obstruction is of a check valve type producing obstructive emphysema, there is hyperresonance with diminution of breath sounds When the obstruction becomes complete there are present all the signs of atelectasis with impaired resonance, distant to absent breath sounds and displacement of thoracic viscera to the involved side

Roentgenologic Findings

If observed when there is partial obstruction of a bronchus roentgenoscopic observation and roentgenograms made at the end of inspiration and expiration should exhibit evidences of obstructive emphysema in the involved lung As a rule these patients come under observation after the obstruction becomes complete when there is retention of secretion and the customary picture is that of obstructive atelectasis with pulmonary suppuration, drowned lung and bronchiectasis

Bronchoscopic Findings

Unlike malignant neoplasms, benign tumors commonly appear as sessile or pedunculated intrusions into the bronchial lumen They tend to conform to the shape of the bronchial lumen and at times appear as finger like pedunculated prolongations They usually are covered with apparently normal mucosa although the degree of vascularity varies with different types of tumor Ulceration is uncommon but erosion of the overlying mucosa often is observed in the presence of suppuration distal to the tumors, there is an absence of fixation, rigidity and deformity of the bronchus as is observed in an infiltrating malignant neoplasm Deformity resulting from atelectatic changes, however, may be present

Diagnosis

While a diagnosis of bronchial obstruction can be made by physical examination and roentgen study of the chest an etiologic diagnosis is possible only by bronchoscopic examination and in the presence of neoplasm by biopsy Since bronchial obstruction may be caused by a number of conditions not neoplastic in origin bronchoscopy and often biopsy are imperative for diagnosis

Biopsies may be secured by using noncutting cup or cutting forceps In true neoplasm cutting forceps usually are required, in polyps and inflammatory granuloma cupped forceps are desirable Biopsy of vascular tumors as adenoma and angioma may give rise to considerable hemorrhage, particularly if a large mass of tissue is secured Pressure with a gauze tipped sponge carrier or placement of a bronchial pack for a brief period usually is effective It is important to obtain an adequate biopsy If the histologic reports are inconclusive biopsy should be repeated If the tissue is reported as inflammatory, all should be removed for further study and subsequent bronchoscopic examinations made for evidences of local recurrences

Treatment

In the earlier days of bronchoscopy when surgical extirpation of a pulmonary lobe or lung was hazardous many benign bronchial tumors were treated bronchoscopically by instrumental removal or diathermy Subsequent studies have revealed, however, that in certain tumors local recurrences were not uncommon and furthermore no provision could be made to care for the bronchiectasis and fibrotic changes which developed secondary to the persistence of prolonged bronchial obstruction Certain tumors as papilloma tend to recur locally or may involve new areas These can be successfully treated by bronchoscopic means although it may require many removals Since new areas may be involved at subsequent recurrences any radical measures are contraindicated Edematous polyps and granulation tissues also are best treated by local removal employing cupped forceps

Adenoma of the Bronchus

Unlike carcinoma which occurs more often in the male sex, adenoma is frequently observed among women, in practically all series of cases reported over 50 per cent have been observed in women The age incidence also is important since a majority of the patients are under 40 years of age, many being in the 20 year group Adenoma accounts for

about 75 per cent of all benign bronchogenic neoplasms While there is considerable difference of opinion regarding its relationship to carcinoma if the cylindroma type of tumor is excluded probably none of the adenomas will be found to be invasive, involving regional lymphnodes or metastasizing to distant organs Adenomas usually are composed of an extra—as well as an intra—bronchial portion joined by a pedicle and are referred to as collar button or dumb-bell shaped

The symptoms of bronchial adenoma are due to bronchial irritation and obstruction Cough is probably the most common symptom and occurs without or with sputum in every case It is irritative in type, worse at night, particularly when the patient assumes a prone posture If pulmonary suppuration is present the cough is like that observed in bronchiectasis Wheezing respiration is an early symptom but often is overlooked by patients When obstruction becomes complete the wheeze disappears Hemoptysis is a common symptom and in about 20 per cent is the initial symptom It often is massive, occurring suddenly and may be very alarming One of its characteristics is its sudden occurrence without any premonitory warning It may occur during the menstrual period

Since adenoma is a slowly growing tumor atelectasis of one or more pulmonary lobes is a frequent roentgenologic observation (Fig 1) Symptoms are commonly of several years duration and diagnoses of atypical pneumonia bronchiectasis pulmonary fibrosis or empyema are not unusual A diagnosis of bronchial obstruction with atelectasis can be made by physical examination and roentgen study but bronchoscopic examination and biopsy are necessary to detect the presence and character of the tumor To determine if there is an extrabronchial extension of the tumor, body section roentgenography is useful

The common bronchoscopic finding is partial or complete occlusion of a bronchus by a relatively smooth pinkish reddish or purplish mass which at times appears fleshy It may be firm or soft As a rule the soft tumor is vascular and bleeds promptly when a biopsy is done Small tumors may appear as sessile elevations and suggest that they are entirely endobronchial Commonly the bronchus is filled with a large mass which appears pedunculated but usually has a fairly large point of attachment

Treatment by irradiation or bronchoscopic implantation of radon has proven unsuccessful The intrabronchial tumor can be treated bronchoscopically by forceps removal or electrocoagulation If there is an extrabronchial portion surgical removal by lobectomy or pneumon

ectomy is necessary Bronchiectasis is a common complication of adenoma, and this too is an indication for surgical therapy

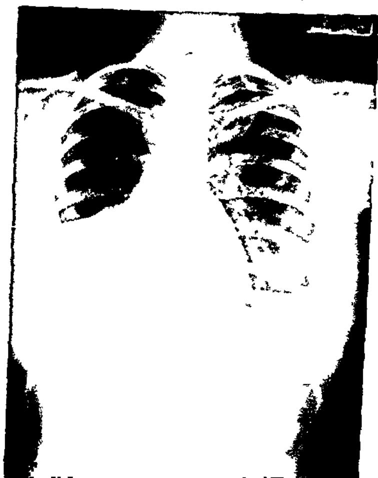


Fig 1 Rc
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Papilloma of the trachea or bronchus more often is observed in connection with papilloma of the larynx and are best removed by using an aspirating bronchoscope as a corer Recurrences are common and therapeutic measures that are destructive to the mucosa should be avoided

because of the danger of cicatricial changes Primary discrete papilloma of a bronchus is best removed with cupped forceps All of the tissue should be subjected to histologic study as carcinoma may occasionally appear as a papillary lesion

Fibroma and *lipoma* usually are not detected until obstruction of a bronchus is complete and complicated by bronchiectasis If detected early removal by bronchoscopy is feasible, if associated with bronchiectasis surgical therapy is indicated

Vascular tumors are very rare If not completely obstructing they are best treated by bronchoscopy and diathermy

Chondroma and *osteoma* may appear as a discrete elevation on a bronchial ring producing variable degrees of obstruction or as multiple small elevations involving a greater part of the circumference of the airway, notably the trachea This latter condition, described as *tracheopathia osteoplastica*, is characterized by the occurrence of hemoptysis A small discrete chondroma can be removed bronchoscopically Large chondromas or osteomas require an external surgical approach The problem of bronchopulmonary suppuration and bronchiectasis, a common complication of benign bronchogenic tumors often is a determining factor in the choice of therapy to be employed

PRIMARY CARCINOMA OF THE LUNG

By SEYMOUR M FARBER, M D AND EDWIN F ALSTON M D

Three hundred years after the first recognizable description of lung cancer by Agricola, a sound histopathologic classification was devised by Virchow and Rokitansky This classification is essentially that used today Following scattered initial reports, collections of cases were published by Eberman, Reinhard and Wolf Adler reported 374 cases taken from the literature to 1912, and since his important monograph, numerous reports on series of 50 or more cases have appeared These emphasize the high incidence of the disease and provide a firm foundation on which diagnosis and therapy are based

General Incidence

Carcinoma of the lung comprises about 1 per cent of all necropsies and about 10 per cent of all cancers found at necropsy Dublin estimates that each year approximately 15 000 patients die of bronchogenic carcinoma in the United States Graham, *et al* estimated that bronchogenic carcinoma accounted for about 0 54 per cent of all cancers found by necropsy in 1895 The present figure of 10 per cent would seem to indicate a twenty fold increase in the incidence since that date Necropsy statistics from all countries show a corresponding increase in the incidence There can be little doubt that lung cancer is more frequently recognized than ever before

Many investigators have concluded that the incidence of bronchogenic carcinoma has increased absolutely as well as relatively On the other hand, Fried and others believe that the increase is more apparent than real, and that it is based on better methods of diagnosis, increased attention to the disease more frequent hospitalization of patients more available medical advice and greater longevity

Although the incidence of bronchogenic carcinoma has increased that of other forms of cancer has remained relatively stable At present bronchogenic carcinoma *is next in frequency* to carcinoma of the stomach and of the large intestine Halpert has predicted that carcinoma of the lung will become the most common malignancy in males

Age, Sex and Race Incidence

All necropsy series present comparable figures regarding age distribution of carcinoma of the lung The disease occurs most frequently in the years between 40 and 70 Farber and Tobias report that in their

200 necropsied cases of bronchogenic carcinoma 90 per cent were in the age group of 40 to 80 Nevertheless, this cancer may occur in younger people Perrone and Levinson have found 13 reported cases of patients *less than 19 years of age*

All series indicate that carcinoma of the lung occurs more frequently among males than females Ochsner, *et al*, analyzing 8,575 collected cases found that 78 9 per cent were males—a sex ration of about 4 1 The age distribution is about the same for men and women Dorn has pointed out that from 1930 to 1940 the death rate from cancer of the lung increased about 80 per cent in males, whereas it increased only 20 per cent in females In all forms of cancer there was a 10 per cent increase in males and 1 per cent increase among females during the same period

Some evidence suggests a higher incidence of bronchogenic carcinoma among whites than among Negroes, but this evidence is by no means conclusive A study by Ochsner indicates that increased incidence of bronchogenic carcinoma in New Orleans occurred primarily in white patients and showed little or no change among colored patients

Occupation

Studies indicate that bronchogenic carcinoma occurs in patients from every occupation Patients doing out door work are about equal in number to those doing indoor work Analysis of cases from the general population does not show any correlation between the incidence of bronchogenic carcinoma and hazardous occupations involving exposure to industrial dusts, chemicals, etc

However, it might be expected that a high incidence of lung cancer occurring in certain industries representing a very small portion of the population would not show up in statistics representing the general population The high incidence of carcinoma of the lung among the miners of Schneeberg in Saxony, Germany, and among those of Jachimov in Czechoslovakia is well known In some series, 50 to 75 per cent of these miners have developed cancer of the lung The report by Machle and Gregorius, on cancer of the lung among workers in seven American chromate plants, provides definite evidence of the occupational origin of these tumors. In a total of 193 deaths from all causes among these chromate workers, 42 (22 8 per cent) were due to pulmonary cancer An excessive incidence of pulmonary cancer has also occurred among

PRIMARY CARCINOMA OF THE LUNG

By SEYMOUR M FARBER, M D AND EDWIN F ALSTON M D

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genic carcinoma As pointed out by Murray, it is likely that some constitutional defect, probably congenital, must be present to pave the way for the deleterious effects of chronic irritation

Gross Pathology

Bronchogenic carcinoma may develop in the larger bronchi or in any one of the more distal branches About three-quarters of the cases are found at or near the hilum Fewer than one-fourth of the cases have a peripheral location The lesion is found somewhat more often in the upper lobes The Pancoast, or superior sulcur tumor, is most often a bronchogenic carcinoma arising from a small apical bronchiole Pulmonary cancer occurs a little more frequently on the right than on the left

Gross pathology of carcinoma of the lung begins as a piling up of the bronchial epithelium The developing neoplasm may project into the lumen of the bronchus causing partial or complete obstruction Often it extends along the bronchus in the submucosa and insinuates itself between the bronchial cartilages causing extensive destruction of bronchial tissue The tumor may grow outward into the lung structure, and form a more or less rounded dense mass with displacement of the adjoining bronchi, or involve large irregular areas of pulmonary tissue Eventually the cancer may extend to surrounding structures, such as the throacic wall diaphragm, pericardium, nerves, great vessels, pleura, etc

The gross appearance of the tumor is variable Usually the cancer is hard and granular, reflecting the cellular character of the tumor with its fibrous stroma, and cross section may be gray-white or pink The margin may be sharply defined, but often fades almost imperceptibly into the surrounding tissue, depending on the density of the neoplastic cells Tumor substance often contains hemorrhagic or necrotic areas filled with pus or mucus The bronchi may fill with papillary projections of tumor and its mucosal surface become necrotic and eroded

Microscopic Pathology

Studies of bronchogenic carcinoma will reveal a mixture of cell types in almost every tumor However, most lung cancers are classifiable as squamous cell carcinoma, adenocarcinoma or undifferentiated carcinoma, according to the predominating cell type (Fig 1)

workers in other occupations, such as asbestos industries, nickel-copper refineries, stokers in generator plants, etc

Etiology

Carcinoma of the lung may occur at any age, in either sex, in persons of all races, and regardless of occupation It may well be that various etiologic factors are at *work in different individuals to produce carcinoma* of the lung It may be concluded that males from the age of 40 to 70 are more exposed to some of these etiologic *factors or more susceptible* to them, or both The apparent increase in the incidence of bronchogenic carcinoma during the past several decades might be a manifestation of a greater exposure or susceptibility to these factors than in previous years

Many diverse factors have been investigated Exposure to radioactive emanations, as observed among the Schneeberg and Jachimov miners certainly seems to have some significance in the development of carcinoma of the lung in these groups The high incidence of cancer among the chromate workers seems to implicate the chromates as carcinogenic agents Bronchogenic carcinoma, occurring with asbestosis, often shows *multicentric foci of origin corresponding in distribution with the asbestosis* bodies Smoking has attracted increasing interest as a possible factor *Important statistical evidence is now being analyzed and its significance* awaits further evaluation

Many chronic pulmonary diseases are often associated with epithelial metaplasia and considered possible precursors of pulmonary cancer In some series there has been a relatively high association of tuberculosis with cancer of the lung, but the concensus is that probably there is no etiologic relationship Chronic lung disease, such as bronchiectasis, abscess pneumonia, etc, *frequently coexist with carcinoma of the lung* In most cases, these diseases seem to be complications of pulmonary cancer *and are thought to be of doubtful significance in the etiology of carcinoma* of the lung At one time it was feared that the influenza epidemic of 1918 would predispose many individuals to lung cancer, but in recent years influenza has not been considered seriously as a cause of this carcinoma

No single etiologic factor can be indicated as the cause of *all* pulmonary cancers Most of the factors studied have the common property of producing pulmonary *irritation It is possible that such* irritation is of the greatest significance in the causal sequence leading to broncho

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Fig 1 Sections showing histopathologic types
A Squamous Cell Carcinoma
B Adenocarcinoma
C Anaplastic Carcinoma

The incidence of the various cell types varies considerably from one series to another Epidermoid or squamous cell carcinoma is most frequently encountered, comprising from 5 to 65 per cent of the bronchogenic carcinomas in various series No definite relation has been observed between the patient's age and the cell type, although Gebauer s series showed older people to have squamous cell carcinoma more frequently Gebauer and Murray have commented that whereas squamous cell and undifferentiated carcinomas are rare in women, adenocarcinoma occurs relatively often, and in Gebauer's series 28 per cent of the adenocarcinomas occurred in women

These three different cell types occurring in pulmonary cancer are considered to develop from one precursor the differentiated multipotential basal cell of the bronchial epithelium Thus, most primary cancers of the lung probably are bronchogenic in origin

Although the different types of carcinoma appear to arise from the same type of cell, the type characterizing any given bronchogenic carcinoma may be associated with more or less specific pathologic and clinical features *These differences are not sharply defined, but may* be of sufficient importance to play an increasing role in choosing the most desirable therapy and in estimating the prognosis

Cell types may arise from any part, but, each cell type tends to favor certain parts of the bronchial tree Most of the small cell carcinomas (undifferentiated) arise from the main stem bronchi, and the remainder from the orifice of the secondary branches, rarely is a small branch bronchus the site of origin Adenocarcinomas usually are more

peripherally located arising in the secondary branches such as the lobar stems, but a few arise in the small bronchi and a few in the main bronchi Often in the early stages of development there is an appreciable gap between the adenocarcinoma and the hilum which may lessen considerably as the mass enlarges The squamous cell carcinomas may occur anywhere along the course of the bronchial tree, but as a rule spring from a point within or near the large branches of the stem bronchus

The squamous cell carcinoma grows slowly and generally remains localized forming a nodular mass around the bronchus Its proximal portion tends to surround and constrict the bronchus whereas the distal portion may invade the lumen further adding to obstruction Areas of keratinization show up as small granular bodies These tumors show a pronounced tendency to necrosis and hemorrhage Various degrees of bronchial ulceration are frequently present

The centrally located undifferentiated carcinoma usually shows the most rapid growth It tends to form an irregular mediastinal mass is highly invasive and extends along the bronchus surrounding it and neighboring structures with firm tumor It may invade the adjacent lung although this process is less conspicuous than its mediastinal extension

Adenocarcinoma grows faster than the squamous cell type but slower than the undifferentiated carcinoma It shows a greater tendency to invade and constrict the bronchus The lining epithelium usually remains intact Because of its tendency to originate in the secondary and small bronchi it may form one or more well circumscribed masses in the peripheral pulmonary parenchyma Occasionally mucous degeneration is present

Secondary Pathology

Much of the secondary pathology depends on the relation of the tumor to the bronchus The cancer may radiate outward from its point of origin and ultimately exert pressure on surrounding bronchi and blood vessels or it may grow into the bronchus and be followed by a variable degree of obstruction

Partial obstruction tends to be relatively greater during expiration than during inspiration The inspiratory force is stronger and during inspiration the bronchus has a greater diameter than with expiration Thus there is a tendency for air to be trapped in the lung segment distal to the point of obstruction Accordingly emphysema often develops as a complication of partial obstruction and there may be displacement of sur



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rounding structures depending on the size of the emphysematous segment

There will be complete obstruction when the lumen is completely filled or constricted by tumor The first consequence will be the development of atelectasis due to diminished intake of air Collapsed areas usually have a triangular shape Secretions accumulate distal to the obstruction, and trapped bacteria may proliferate and produce extensive inflammatory process Thus, bronchiectasis and pneumonitis may develop The pneumonitis may be extensive, often completely overshadowing the neoplastic process

Eventually abscesses and cavities may develop in response to infection, tumor necrosis, obstruction, interference with blood supply, etc Abscesses are relatively prominent in the secondary pathology of carcinoma of the lung, occurring in as many as half of some series Epidermoid carcinoma seems to be more frequently accompanied by abscess formation than other types (Fig 2)

Frequently pleural effusions occur as a reaction to irritation caused by inflammation, extension of the carcinoma to the pleural surface, etc Farber and Tobias found a pleural effusion in 26 5 per cent of their series of 200 It was clear in 18 9 per cent and bloody in about 8 per cent of the total number of cases



Fig 2 Abscess and cavity secondary to squamous cell carcinoma

Further complications may develop from extension of the cancer to surrounding structures, such as the pericardium heart, great vessels and thoracic wall The tumor occasionally surrounds and compresses the superior vena cava causing obstructions, thrombosis, and development of collateral circulation

Metastases

Bronchogenic carcinoma shows a pronounced tendency to invade vascular and lymphatic channels Tumor cells from lung cancer, after invading the pulmonary veins, may be disseminated from the left side of the heart to any part of the body This is unlike the blood stream metastases of other cancers which are usually filtered out of the circulation by the liver and lungs The lymphatic distribution of the thoracic cavity, con

necting with thoracic and abdominal tributaries likewise permits a widespread distribution of metastases. Thus metastases from carcinoma of the lung often are more widespread than those of any other type of cancer, and the extent to which the body may be involved is well illustrated in the following table.

METASTASES

Organ	Squamous	Und'ff	Adenoca	Unclass	Total
Bronchial Nodes	57%	73%	56%	40%	63.5%
Liver	22%	47%	42%	20%	37.5%
Adrenals	18%	41%	29%	0%	30.5%
Mediastinal Nodes	23%	26%	27%	20%	25%
Pleura	15%	30%	31%	0%	25%
Bone	22%	29%	22%	20%	25%
Other Lung	13%	23%	27%	20%	21%
Kidneys	18%	20%	18%	0%	18.5%
Brain	7%	19%	29%	20%	*17.5%
Ribs	18%	17%	16%	20%	17%
Supraclavicular Nodes	17%	13%	18%	0%	15%
Vertebral Column	7%	20%	9%	20%	13.5%
Abdominal Nodes	5%	17%	13%	0%	12%
Pericardium	18%	7%	11%	20%	11.5%
Tracheocervical Nodes	5%	16%	11%	0%	11%
Myocardium	10%	11%	11%	0%	10.5%
Epicardium	8%	10%	9%	0%	9%
Pancreas	2%	11%	4%	0%	6.5%
Diaphragm	7%	4%	7%	0%	5.5%
Small Intestine	8%	6%	2%	0%	5.5%
Skin & Subcutaneous Tissue	5%	3%	11%	0%	5.5%
Spleen	3%	6%	4%	20%	5.0%
Bone Marrow	2%	7%	2%	0%	4%
Thyroid	0%	4%	7%	0%	3.5%
Gall Bladder	2%	3%	2%	0%	2.5%
Esophagus	3%	2%	2%	0%	2.5%
Omentum & Mesentery	0%	4%	0%	0%	2%
Large Intestine	2%	1%	4%	0%	2%
Peritoneum	0%	2%	2%	0%	1.5%
Skull	2%	1%	2%	0%	1.5%
Long Bones	0%	1%	4%	0%	1.5%
Rec. Laryngeal Nerve	2%	1%	2%	0%	1.5%

male patient over the age of 40 Furthermore, if there are symptoms referable to other parts of the body associated with thoracic symptoms a suspicion of carcinoma of the lung should be considered It must always be borne in mind that carcinoma of the lung may occur in either sex and at any age The course of carcinoma of the lung should be considered as rapid, and any pulmonary complaints should be analyzed by every available method to determine its underlying pathology The earlier the diagnosis, the greater the hope for effective therapy

Roentgenography X ray has proved one of the most helpful of of all methods in the diagnosis of pulmonary disease, including bronchogenic carcinoma (Fig 3) Most cases will show some pulmonary pathology A presumptive diagnosis of pulmonary cancer may be made by x ray in more than half of the cases Following induction of artificial pneumothorax, x ray may yield a better outline of the growth a better appreciation of its size, and a clearer picture of complicating lesions Needless to say, roentgenograms taken at various angles will heighten the percentage of correct diagnosis If pleural effusion or thickening are present, it is well to take over exposed x rays to reveal the underlying pathology



Fig 3 X rays show
A Squamous Cell Carcinoma
B Adenocarcinoma
C *Anaplastic Cell Carcinoma*

Fluoroscopy may be helpful, revealing an elevated diaphragm on the side of the tumor, paradoxical respiration, swing of the heart toward the affected side during inspiration or away during expiration and absence of expansile pulsation if the mass is located near the arch of the aorta

Tomography is useful in clearly delineating the mass or cavity

within, and in locating the exact position of the growth relative to the anterior-posterior planes

Bronchography may be valuable for demonstrating intrabronchial tumors or bronchial stricture However, it presents the danger of trapped iodized oil which may excite the inflammatory process, obscure roentgenographic and bronchoscopic procedures, and delay possible surgical intervention Many observers express the opinion that tomography adequately serves the purpose of studying intrabronchial tumors and does not have the unsatisfactory features of bronchography

The most frequent findings by x-ray and auxiliary procedures, consist of atelectasis, increased pulmonary markings, tumor mass, abscess or cavitation, pleural effusion These features are, of course, determined by the size and location of the tumor, the obstruction it produces and the character of its extension

According to Gebauer the radiologic features of the various histologic types vary somewhat and may justify a suspicion of the type of bronchogenic carcinoma Squamous cell carcinomas usually spring from or near the hilum and arch out in a semicircular contour into the body of the lung, the periphery may have strands radiating out into the parenchyma These may be associated with such inflammatory infiltration, atelectasis, necrosis, and cavitation of the primary tumor The small cell carcinoma shows an early irregular, poorly defined mass blending with the mediastinum It enlarges rapidly extending to the mediastinum producing distortion of the structures The adenocarcinoma usually presents a rather dense mass in the parenchyma away from the hilum, although occasionally it appears in the mediastinal half of the lung field These masses usually are sharply circumscribed Later in the development of the disease, secondary tumor nodules often occur in the lung field Adenocarcinoma rarely occurs as a mediastinal tumor mass simulating a small cell carcinoma, sometimes it cavitates, suggesting squamous cell carcinoma

X-ray studies may lead to a strong presumptive diagnosis of lung cancer, and in some cases the findings may even suggest the cell type Nevertheless, carcinoma of the lung may simulate other pulmonary diseases and these often simulate carcinoma It is impossible, therefore, to make an absolutely positive diagnosis until the tumor is removed and its pathology identified under the microscope

BRONCHOSCOPY Bronchoscopy often makes it possible to visualize a tumor, or to observe fixation, deformity, blood, or purulent discharge. It offers a simple and effective means of obtaining a biopsy in many

cases It must be remembered that about 20 per cent of bronchogenic carcinomas are either in the periphery of the lung or in the upper lobe bronchi beyond the visual angle of the bronchoscope In some cases as high as 98 per cent of these centrally located tumors have been viewed and biopsied by means of the bronchoscope In many cases, although the tumor itself cannot be visualized, fixation, blunting and hardening of the carina are sufficient to make a presumptive diagnosis of malignancy Another procedure, the aspiration of bronchial secretions for cytologic studies, will be discussed later In addition to aiding in the diagnosis of bronchogenic carcinoma, bronchoscopy may also provide information about the operability of the lesion If there is local intrabronchial extension to an unresectable area of the tracheobronchial tree, or if there is extensive peritracheal lymph node involvement, these can best be detected by bronchoscopy

A negative bronchoscopy does not rule out the existence of carcinoma Many cases which are negative at bronchoscopy probably would have a better prognosis if, by *some other means, they could be recognized* early As pointed out by Gebauer, successful bronchoscopies often are performed on patients with an advanced stage of the disease

Cytologic Diagnosis

Recently attention has been focused on a simple method of suggesting, establishing or confirming the diagnosis of bronchogenic carcinoma As most primary carcinomas of the lung originate in the bronchus, cells *from the surface of the tumor* exfoliate into the lumen and are expectorated with the bronchial secretions With adequate cytologic technique and knowledge of the cellular components of bronchial secretions, neoplastic cells have been repeatedly demonstrated in 90 per cent of proved cases

Method of Preparing Slides Material must be carefully obtained and slides properly prepared in order to preserve the cytologic detail essential for the recognition of malignant cells and differentiation of them from the normal cellular flora of sputum or bronchial secretions If sputum is to be examined the patient is instructed to raise secretions from the lower part of the respiratory tree Smears should be made immediately to avoid loss of cellular detail by autolysis If there is to be a period of time before slides are prepared and fixed it is best to have the sputum expectorated into jars containing 10 cc. of the fixative solution Sputum should be examined in a Petri dish against a dark back

ground. Various suspicious components of the sputum such as tissue fragments or blood flecks are selected, using a magnifying glass if necessary, and are gently smeared over two-thirds of the slide. Pressure will cause distortion during this procedure. Thick smears are not suitable for the study of cytologic detail. It is important to immerse the smears in the fixative solution while they are still wet. This fixative solution consists of equal parts of ether and 95 per cent ethyl alcohol. A paper clip attached to alternate slides will separate the smears.

Bronchial secretions obtained at bronchoscopy are treated in the same manner. Secretions should be obtained from suspicious areas of the bronchial tree for preparation of slides. If secretions are very scant, all material should be saved.

After fixation for a two-hour period, slides may be removed from the solution and permitted to stand, protected from dust, for at least seven days before staining. This permits mailing of slides to laboratories where trained personnel can examine the smears.

Smears are stained by the Papanicolaou technique. A description of this technique has appeared in several recent monographs. It is not necessary with this technique to control the nuclear stain with microscopic observation as it is with hematoxylin and eosin.

Nonmalignant Components

The nonmalignant components of sputum and bronchial secretions are epithelial cells, cells from the blood and cells from the reticulo-endothelial system. Epithelial cells include ciliated columnar cells from the trachea and bronchi. Squamous cells originate in the mouth, pharynx, and occasionally in areas of metaplasia in the lower part of the respiratory tree. Blood elements which may be observed include erythrocytes, polymorphonuclear leukocytes, lymphocytes, monocytes and occasionally megakaryocytes. The reticulo-endothelial system contributes macrophages (histiocytes) and giant cells. Macrophages may exhibit marked pleomorphism. They may be mistaken for malignant cells, particularly when they do not contain phagocytized particles. Careful and thorough study of sputum from patients suffering from various types of nonmalignant respiratory disease is a necessary prerequisite in the study of smears for neoplastic cells (Fig. 4).

Malignant Components

Neoplastic cells found in the sputum and bronchial secretions may be classified as differentiated and undifferentiated. Differentiated

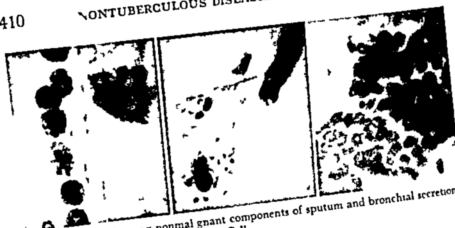
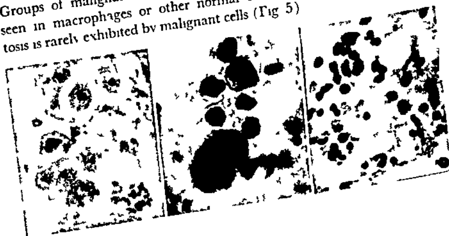


Fig 4 Smear showing nonmal gnant components of sputum and bronchial secretions
A Macrophages and Squamous Cell
B Squamous Cell and Ciliated Columnar Cell
C Sheet of Columnar Cells

neoplasms in the lung include squamos cell (epidermoid) carcinomas and adenocarcinomas It is not always possible to assign one lone cell to the appropriate classification but when groups of malignant cells are seen it may be possible to classify them Usually the average malignant cell is large, but it need not be particularly if it is exfoliated from anaplastic carcinomas The nuclear cytoplasmic ratio often is large and at times the nucleus may appear to be naked The nuclei may attain excessive size, vary in shape and position, and one cell may have more than one nucleus This variability is noted particularly when various malignant cells are compared The chromatin usually is arranged in irregular fragments or in a course meshwork Mitotic figures may be observed Nucleoli vary in size, shape and number from one cell to another Groups of malignant cells may be crowded together in a manner not seen in macrophages or other normal cellular components Phagocytosis is rarely exhibited by malignant cells (Fig 5)



Results

In the authors' series, 6,281 sputum or bronchoscopically obtained specimens from 2,066 patients have been submitted. Malignant cells were found in 55 per cent of 241 cases which later proved to be carcinoma of the lung. When a complete series of five sputum specimens were received, the accuracy of cytologic diagnosis was increased to 90 per cent. In examining both sputum and bronchoscopically obtained smears from the same case, the accuracy has been comparable.

Cytologic diagnosis is being accepted by an increasing number of pathologists and clinicians. The diagnostic significance of some cells has yet to be determined, and further study will make the identification of the cytologic elements more precise. As experience is acquired and the criteria more clearly established, the percentage of accurate positive results increases. However, the present trend of popularization of cytologic diagnosis of cancer carries certain inherent dangers. It must be strongly emphasized that considerable experience is necessary before malignant cells can be distinguished from certain nonmalignant cells. This cannot be acquired by an occasional examination of smears from the various exudates in the body.

Treatment and Prognosis

Untreated carcinoma of the lung inexorably leads to death, usually within one year. Rarely does a patient survive the ravages of the disease for a longer period, but very unusual patients have lived as long as ten or more years without treatment. The survival period is often slightly longer for patients with squamous cell carcinoma than for those with adenocarcinoma or undifferentiated carcinoma (Goldman).

Surgery, with complete removal of all cancerous tissue, offers the only hope. Even so, only if the diagnosis has been made shortly after onset of the disease can surgery be expected to accomplish a cure.

Operation is indicated if there is a reasonable chance of removing the cancerous tissue. It is contraindicated if there is evidence of extension, as manifested by pleural effusion, metastases to lymph nodes or other organs of the body, the apical syndrome, nerve paralysis, etc. Often extension is discernible only after thoracotomy. When extension

Fig 5 Smears of sputum and bronchial secretions showing
A Malignant Squamous Cells.
B Adenocarcinoma Cells.
C Anaplastic Cells

of carcinoma of the lung renders curative surgery impossible, operation might still be indicated in order to make the patient more comfortable spare him sepsis, continued exudation, etc In some instances the survival period following palliative resection is sufficiently long to justify operative surgery

Total pneumonectomy is the procedure of choice. The technical considerations for this procedure are dealt with at length by other authors The results must be evaluated from many points of view Analyzing 1,950 collected cases, Churchill found that thoracotomy was done on 782 patients (40 per cent) and resection on 432 cases (22 per cent) The operative mortality rate has become progressively less with the adoption of new techniques and supportive measures In 1944 Rienhoff reported an immediate mortality rate of 21 per cent in 71 operated cases He prophesied that with earlier diagnosis improved technique and antibiotics the mortality rate would be reduced to about 15 per cent Jones reported a total of 52 pneumonectomies performed from 1943 to 1947, with an operative mortality rate of two patients (4 per cent) In 1947 Adams reported 30 consecutive resections performed on 31 4 per cent of his patients with a hospital mortality rate of 3 3 per cent These figures are comparable with those of the operative mortality rate for total gastrectomy in the case of malignant lesions of the stomach

Ochsner, *et al*, report that 23 3 per cent of the patients operated on five years previously were still alive, which indicates a five year survival rate of 8 per cent for all their cases of bronchogenic carcinoma These results are comparable with the results achieved by surgery for gastric carcinoma The efficacy of operation in some cases of bronchogenic carcinoma may be evaluated by another method as wisely pointed out by Churchill 'It is probably more informative to consider that Graham s patient in whom a total pneumonectomy was performed for squamous cell carcinoma in 1933 is still alive and well than it is to attempt to interpret the preliminary analyses that have been placed on record

X ray therapy offers very little, if any, hope for cure In some cases it may be used as a palliative measure offering much relief from symptoms and occasionally prolonging life Most observers agree that x ray therapy is contraindicated when operation may be effective Advanced cases with lung necrosis, inflammation, empyema probably are

made worse by intensive irradiation, and should be treated surgically, if at all

Comment

There are inherent difficulties in the diagnosis of carcinoma of the lung. Of these, the most important is the paucity of symptoms and signs during the early stages. Yet, even when symptoms and findings suggesting the nature of the process are present, the clinician may still be left in doubt by accepted diagnostic procedure. Cytologic studies are of value in many instances, but, further evaluation under rigid investigative control is necessary before this technique can take its proper place, and an important point in this evaluation will be to determine the number of patients that will have successful removal of the involved lung after malignant cells have begun to exfoliate in the bronchial secretions. Certainly more diagnostic aids must be found for the early recognition of bronchial carcinoma. Observation of early physiological changes and the use of radioactive products may add to our diagnostic facilities.

In the meantime, physicians must become increasingly aware of the masquerading tendencies of bronchogenic carcinoma. Dissemination of knowledge and early accurate diagnosis must keep pace with the development in surgical thoracic techniques.

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PULMONARY ADENOMATOSIS

By ANDREW L. BANYAI, M.D. AND J. WINTHROP PEABODY, M.D.

Pulmonary adenomatosis occupies a unique place in clinical medicine as well as in the science of pathology. Although the first case was reported almost half a century ago by Helly in 1907 the number of authentic reports is still very few today. This, however, does not necessarily imply the actual rarity of this disease. Rather, it may be due to lack of its recognition at the bedside. It is known that there exists possibility of exposure to a communicable pulmonary disease in sheep and some other animals the pathologic manifestations of which seem to be identical with those seen in human beings. There are certain geographic locations where this condition is common in animals. These include South Africa, England, France, Iceland and Montana in this country. It is called "Jaagziekte," "drive sickness," "verminous pneumonia," "la bouhite," "epizootic adenomatosis," "progressive pneumonia," or "lunger disease." The prevalence of the disease in sheep is well documented by records showing that during some of the epizootics more than half of the affected herd was lost. Considering that it is transmissible from diseased animals to man, it is likely that with keener diagnostic consciousness, more clinical cases of this disease will be recognized in the future, unless human beings in close contact with infected animals possess a high degree of resistance to this disease. A case in point is that reported by Hildebrand. His patient was a ranch wife who lived most of her life on a large sheep ranch in Montana. Although for several years prior to her last illness she lived in town, she visited the same ranch frequently and spent her vacation there shortly before the onset of her pulmonary adenomatosis. Jaagziekte was known to be prevalent in the sheep there. One of the animals with signs and symptoms of the disease was killed and necropsy confirmed the diagnosis.

Pathologically, human pulmonary adenomatosis is found in five forms. (1) Lobar or multilobar involvement with lobulated, granular induration which is localized in one or both lungs. (2) Large, sharply demarcated, spherical mass, the size of an apple or larger, which involves the parenchyma of one lobe. (3) Widespread patchy induration, unilateral or bilateral. (4) Miliary nodules of elastic consistency, resembling noncaseating tubercles. (5) The combination of these changes presenting one type of lesion in one lung and another type in the other. Also, the various forms may be encountered simultaneously

on one side Masses of pulmonary adenomatosis which belong in the first and second categories may show a necrotic center with the formation of a cavity of considerable size

As to histologic characteristics of this condition, we quote the findings of Wood and Pierson "All sections showed a striking hyperplasia of columnar epithelial cells which focally lined various alveoli These foci showed varying degrees of proliferation with the formation of intra-alveolar papillary and cystadenomatous masses of columnar cells In places a single row of columnar cells lined the alveoli In all areas careful study revealed apparent preservation of alveolar stroma The cells varied from low to tall columnar and were nonciliated Their cytoplasm was finely granular and moderately eosinophilic Occasional cells showed nuclear inclusion bodies Quite uniformly, the nuclei were pale, presenting finely reticulated chromatin Although a majority of nuclei were basal in position, many were mesially placed Mitotic figures were extremly infrequent In the areas of slightest involvement the only change present seems to be that which involved the epithelium No inflammatory or stromal changes existed in such areas In larger areas, however, small numbers of loosely scattered lymphocytes and plasma cells occurred in the stroma There was also a mild perivascular collaring by similar cells No apparent relationship existed between the inflammatory foci and the masses of hyperplastic alveolar cells Occasional, otherwise normal alveoli contained desquamated septal cells, mononuclear phagocytes and very occasional polymorphonuclear leukocytes In none, however, was there fibrin or definite exudate Sections of the peribronchial lymph nodes showed a moderate deposition of anthracotic pigment, but no tumor cells Adjacent bronchioles showed no papillary or proliferative changes of their lining epithelial cells Contained within their lumina was a mucinous substance which contained not only occasional mononuclear phagocytes but also moderate numbers of columnar epithelial cells These had the appearance of desquamated epithelial tumor cells"

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nosis on account of the frequent mitosis he observed in the exuberantly growing alveolar lining cells Simon (1947) regards pulmonary adenomatosis as primary alveolar cell carcinoma According to Delarue and Graham, pulmonary adenomatosis is alveolar cell carcinoma of multicentric origin Contrary to this opinion and the findings of others, Paul and Ritchie noted evidence that the hyperplasia of the alveolar lining originated from bronchiolar epithelium rather than from alveolar covering cells When carcinomatous metamorphosis develops, metastasis may take place Swan expressed the view that although the neoplastic growth designated as pulmonary adenomatosis appears histologically noncancerous, clinically it must be considered cancerous As a complication of pulmonary adenomatosis, clinical or postmortem examination may reveal atelectasis, emphysema, bronchiectasis, abscess or bronchopneoumonia in areas adjacent to diseased portions of the lung

Pulmonary adenomatosis has been observed in adults only Most of the cases occurred in middle-aged or old persons So far, the etiologic agent of the disease has not been identifed Cowdry (1925), Bonne (1939), Taft and Nickerson (1944), Wood and Pierson (1945) and Dungal (1946) consider it of virus origin

Symptoms

Clinically, it is a chronic disease with an insidious onset In some instances a previously latent disease may become manifest after an acute respiratory infection Its most characteristic symptom is gradually progressive dyspnea In the beginning dyspnea is trivial and does not interfere with the patient's daily activities Subsequently, however, it may completely incapacitate him so that he becomes a bedridden respiratory cripple Dyspnea results from functional insufficiency of the lung brought about by the extensive hyperlasia of the lining of the alveoli In consequence of this oxygen intake is greatly reduced Cough is another prominent symptom It is constant and it is either unproductive or followed by the expectoration of slight, moderate or large amounts of thin, watery, frothy mucoid sputum The latter may be blood streaked There is a noticeable increase in cough on exertion Also, the patient may complain of pain in the chest, usually corresponding to the site of massive involvement The pain is exaggerated on coughing and may radiate to the arms Anorexia may be present and followed by considerable loss of weight Other symptoms that may be noted include weakness, occasional fever and nightsweats Superimposed pulmonary

infection is associated with the well known local and constitutional symptoms It is well to bear in mind that small, circumscribed, solitary lesions of pulmonary adenomatosis may occur without symptoms In one such case found on routine x ray examination the condition was identified on histologic examination after lobectomy The patient of Meade and his associates (1947) presented himself with symptoms and signs of bronchiectasis Following lobectomy, microscopic studies revealed unsuspected adenomatosis

Diagnosis

Patients in the advanced stages of the disease are found to be dyspneic on slightest exertion and are cyanotic The fingers show marked clubbing Moderate or high fever accompanies superimposed pulmonary infection Physical findings over the chest are predicated upon the type and extent of the lung lesion In patients with massive unilateral involvement, there is limitation in respiratory motions of the chest on the respective side In addition one finds dullness, bronchial or distant breath sounds and numerous fine moist rales over the diseased area In general the findings closely resemble those of lobar pneumonia

Dennis and his associates following a review of the literature note that adenomatosis should be suspected in cases with (1) chronic pulmonary disease in which there are repeated attacks of acute pneumonia (2) a nonspecific patchy or homogeneous infiltration on roentgenologic examination and (3) the production of a large amount of thin, watery mucoid soapsuds like sputum

Roentgenologic findings vary according to the character of the pulmonary process They are (1) unilateral or bilateral homogeneous densities occupying the area of one or more lobes (2) sharply circumscribed heavy, dense round shadow the size of an apple or larger situated in one lobe (3) soft patchy shadows, with ill-defined irregular outlines giving the appearance of multiple small bronchopneumonias in both lungs, (4) widespread miliary nodules with indistinct borders (5) combination of the various forms localized in either lung or bilaterally

Interpretation of the x ray findings must be done with a great deal of thought, for a number of other conditions may cast similar shadows It is mandatory, therefore to rule out such conditions, including lobar and bronchopneumonia caused by pneumococci, tubercle bacilli, fungi and other pathogenic micro-organisms. When a massive round shadow

is seen on the roentgenograms, one should keep in mind the possibility of one of the following conditions

Pulmonary abscess
Lung tumors
benign
malignant
primary
metastatic
Sarcoidosis of hilar lymph nodes
Teratoma
Mediastinal tumors
Encapsulated pleural effusion
Tumors of the pleura
Tumors of the thoracic wall, including the diaphragm
Solitary, fluid filled cyst of lung or mediastinum
Thoracic gastric cyst
Cold abscess
Diaphragmatic hernia
Subdiaphragmatic tumors casting x ray shadow in lower lung field
Aneurysm, aortic, cardiac, pulmonary, innominate or intercostal artery
Pulmonary arteriovenous aneurysm
Epicardial fat pad
Diverticulum of the esophagus
Hodgkin's disease
Polycythemia vera
Pulmonary hematoma with subsequent fibrosis
Large gumma
Massive lesion caused by fungus
Large tuberculoma
Echinococcus cyst
Infarction

Miliary shadows widely distributed in both lungs obligate one to take into consideration diseases which are known to be associated with similar x ray pictures A list of these conditions is given in the chapter on Pleuropulmonary Manifestation of Lupus Erythematosus

In case of doubt, it is permissable to resort to x ray irradiation as a therapeutic test Lymphoblastomas including Hodgkin's disease, respond favorably to such measure No regression of pulmonary ade-

nomatosis follows deep x ray therapy In some instances, exploratory thoracotomy may be found the only expedient diagnostic method

Cytologic studies may be of help in arriving at a correct diagnosis Hematologic examination shows secondary anemia or no deviation from normal except when superimposed infection is present Moderate or marked leucocytosis and an increase in the number of neutrophile leucocytes with a shift to the left in the Arneth or Schilling count are the usual findings in such cases

Prognosis

Duration of the disease varies from several months to eight years It has an inevitably fatal termination The latter is usually due to secondary pathologic changes in the lung induced by pathogenic micro-organisms In certain instances surgical intervention may save the patient s life

Treatment

Supportive and symptomatic measures are called for in cases with widespread bilateral lesions Massive involvement localized in one lobe when the balance of the lung is not affected is best treated by lobectomy This operation was successfully carried out as reported by Wood and Pierson Effler and his associates Meade and his associates and Drymalski and his co workers A patient receiving segmental pulmonary resection as observed by Peterson and Houghton was still alive after 2 and one half years with no evidence of recurrence of adenomatosis

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LYMPHOMATOID DISEASES OF THE CHEST

By Andrew L. Banyai, M.D. and J. Winthrop Peabody, M.D.

It must be a revelation to the sophisticated, and a consolation to the uninitiated to read the enlightening pointed remarks of Willis (1948) on the mass of eponyms which often block the way to a clear comprehension of this subject. He said:

> Nowhere in pathology has a chaos of names so clouded clear concepts as in the subject of lymphoid tumors. As in so many other fields of pathology, this confusion has resulted largely from failure to recognize frankly certain intrinsic difficulties in the subject and to apply certain general principles in their elucidation.

Indeed, the justifiable lament of purists is appreciated when one recalls that in 1933, Wallhauser listed 50 different names for Hodgkin's disease alone.

The cardinal characteristic of all lymphomatoid diseases is that they originate from the reticulum cells of the reticuloendothelial system. After due thought to the available system of classification of these conditions, we have found it expedient to discuss the matter in accordance with the subgrouping offered by Willis:

1. Follicular lymphoma—Localized benign lymphoma
   Multiple follicular lymphoma or lymphosarcoma
2. Lymphosarcoma—Lymphocytoma (Lymphocytic sarcoma)
   Lymphoblastoma (Lymphoblastic sarcoma)
3. Hodgkin's disease
4. Reticulum cell sarcoma

It is well to mention some pertinent comments at this point. Multiple follicular lymphoma is often referred to as Brill-Symmers disease on the basis of the fundamental investigations of Brill and his associates in 1925 and those of Symmers published in 1927. Other eponyms frequently applied to this pathologic condition are: Giant follicular lymphadenopathy, giant lymph follicle hyperplasia, follicular lymphoblastoma and follicular lymphadenopathy. With reference to lymphoblastic tumors, Willis expressed the view that lymphocytic leukemia is not a species of this disease but merely a concomitant of these neoplasms. Hodgkin's disease is also designated by some as lymphogranuloma, lymphadenoma, scirrhous lymphoblastoma and fibro-myeloid medullary

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As to the relative incidence of lymphomatoid diseases, the analytical studies of Jackson can be quoted He found that to every 25 cases of Hodgkin's granuloma, there were 10 cases of reticulum cell sarcoma, six cases of lymphosarcoma, and five cases each of Hodgkin's paragranuloma, Hodgkin's sarcoma and giant follicular lymphoma

Pathology

Hodgkin's disease was first distinguished as a special clinical and pathologic entity by the English physician whose name is associated with it, Thomas Hodgkin, in 1832 It is a more common condition than generally appreciated In general hospitals, 0 25 per cent of all deaths is due to Hodgkin's disease It occurs at all ages, including infancy and senescence and in all races The youngest patient on record is that of Priesel and Winkelbauer, a four and one-half month old infant, in whom the disease was present since birth It is most frequent between the ages of 21 and 30 years The incidence is much higher in males than in females, the ratio varying from 2 5 to 1, to 7 to 1. Instances of familiar occurrence of the disease have been reported Parents and children or siblings of the same family may be affected

Concerning the pathogenesis, the prevalent concept is that Hodgkin's disease is a malignant tumor of the reticuloendothelial system *In spite* of incontrovertible proof to this effect, there are still some obstinate and

tardy thinkers who, on the basis of fallacious interpretation of observations, attribute Hodgkin's disease to infection possibly with diphtheroid microorganisms, tubercle bacilli, Brucella melitensis, the virus of common cold, and others. Proof of the etiologic influence of any of them is lacking. Occasionally, swelling of the cervical lymph nodes due to Hodgkin's disease has been noted after an upper respiratory infection. This chronologic relationship was interpreted by some as prima facie evidence of causal connection. The latter, however, is far from being true. Other items which have been blamed as probable trigger factors in the initiation of the disease include allergic states, the sulfonamides, vaccines used for immunization and others. Among the long assortment of potentially harmful influences male and female climacteric has been dragged in too only to aid the general but needless confusion. Climacteric is a well known scapegoat for many afflictions to which human flesh is heir.

The protean manifestations of Hodgkin's disease are as well recognized as they proverbially apply to syphilis. Its most common form is enlargement of the superficial lymph nodes and the spleen. Splenomegaly is noted in two-thirds of advanced cases. The most frequent site of involvement is the neck; next in order are the inguinal and axillary regions. Bone lesions are found in from 10 to 15 per cent of the cases. Mediastinal lymph nodes are often involved. Carache recorded a 72 per cent incidence in children. Pathologic changes are found in the chest in from 50 to 95 per cent of the cases. The incidence of pulmonary involvement varies from 40 to 60 per cent. Wilks of England is credited as being the first to describe Hodgkin's disease of the lung in 1856. According to Verse primary pulmonary Hodgkin's disease occurs in 10 per cent of all cases. Pleural effusion attributable to this disease is seen in about 5 per cent of early cases and in more than 10 per cent of patients with advanced disease. Formation of hydrothorax is attributed to two causes:

(1) Massive mediastinal lymph node involvement may compress the azygos or pulmonary vein and lead to stagnation of blood in their tributaries.

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Reed cells, by virtually all high priests of Pathology This is done in the face of the chronicles of medical history which tell us that the first description of these cells by Greenfield of Great Britain, was recorded 20 years before the report of the Austrian Sternberg, and nearly a quarter of a century prior to the communication of Reed of Baltimore

The proposition of Jackson and Parker for the recognition of various types of Hodgkin's disease is gaining acceptance Although it is true that it is easier to deal with this condition as a uniform clinical entity, we feel there is no room for dogmatic generalization when critical distinction of different forms of the same disease offers practical advantages This holds true of the classification introduced by these authors The subgroups of Hodgkin's disease are (1) Paragranuloma, (2) Granuloma, and (3) Hodgkin's sarcoma The various types occur at different ages, have different symptoms, respond to treatment differently, and therefore, there is a difference in their prognosis Paragranuloma is less frequent than granuloma It is an early manifestation of the disease It may occur from infancy to extreme old age Microscopically, it is characterized by lymphoid hyperplasia with the predominace of adult lymphocytes and by relative scarcity of giant cells It runs a comparatively benign course and is likely to respond to x-ray irradiation Granuloma is the most frequent form of Hodgkin's disease which may occur at any age Its histologic picture shows eosinophilia, necrosis and fibrosis in addition to the giant cells Its prognosis is more unfavorable than that of paragranuloma Even so, x-ray therapy may bring about satisfactory improvement According to Jackson, Hodgkin s sarcoma never appears before the age of 25 It is more frequent in the fifth and sixth decades The distinguishing features of its microscopic appearance are the predominance of giant cells and large tumor cells It has a grave prognosis Its response to x-ray therapy is far less consistent than that of the two other groups. It is well to bear in mind that paragranuloma may change into granuloma and the latter, rarely, into Hodgkin s sarcoma But, a reverse metamorphosis never occurs

Damage to the reticuloendothelial system in Hodgkin s disease is reflected by the insufficiency of the immuno-allergic function of the body Dubin found statistically significant difference in the incidence of positive serologic test for syphilis in his Negro patients in relation to Hodgkin s disease He reports that 30 per cent of individuals without Hodgkin s disease had a positive Wassermann test, as compared with 16 7 per cent in patients with Hodgkin s disease Also, he found only 2 6

Lymph nodes involved by *Hodgkin's disease* are of firm, rubbery or fleshy consistency Their cut surface is grayish white or yellowish, with more or less fibrous strands It may show areas of caseous necrosis, an appearance which often led to the mistaken diagnosis of tuberculosis in the early days There are six types of pathologic changes in pulmonary Hodgkin s disease

1 Spread of the process from hilar lymph nodes after rupture of their capsule In this manner, a direct infiltration of numerous adjacent alveoli develops

2 Progression of the disease from the hilar lymph nodes takes place along the interlobular, peribronchial and perivascular lymphatics in a fan like fashion

3 Miliary nodules evenly distributed throughout both lungs may closely resemble miliary tuberculosis in their gross appearance Some times such small nodules are found localized in a limited area of the lung and develop in association with other forms of the disease

4 The lung tissue may be replaced by solid, raised, grayish, homogeneous, sharply demarcated masses which measure from 10 to 30 milli meters in diameter Such involvement may be encounterd as a solitary or multiple tumor The latter form may be situated in diverse areas of the lung

5 Massive involvement may occupy the entire extent of one or two lobes Its cut surface shows a heavy reticulum, scanty fibrous tissue and areas of necrosis At the same time, the opposite lung may be entirely free of disease

6 Combination of these forms may be seen on clinical or post mortem examination Necrosis in areas of massive involvement may lead to cavity formation which, on x ray inspection, may easily be in terpreted as suggestive of tuberculosis Massive lesions in the medias tinum may lead to bronchial occlusion, atelectasis and lung abscess In volvement of the bronchi was observed in a patient by Smith and Shefts

Microscopic examination of the lung in Hodgkin s disease reveals that there is an actual infiltration of the affected areas The compon ents of the infiltrations are conspicuous by their pleomorphism The alveoli as well as the supportive tissues of the lung are filled with lym phocytes, plasma cells and characteristic mononuclear or multinuclear giant cells The latter are more numerous in the advanced stages of the disease These cells should be properly designated as *Greenfield cells* but they are habitually, though erroneously, called *Sternberg or Dorothy*

removed specimen showed the histologic characteristic of lymphocytic sarcoma Cutler reported a case of lymphosarcoma of the lung out of a series of 30 patients with this disease, and O Donnell observed two instances To this we can add two cases from our own experience In one of these the clinical diagnosis was confirmed by postmortem examination in the other by exploratory thoracotomy

The mediastinal lymph nodes may serve as the primary site of lymphosarcoma From here it may spread to the lung Such direct extension was described by Falconer and Leonard in 27 2 per cent of their cases They noted hilar lymph node involvement with intrabronchial and peribronchial spread just as frequently more or less lobar spread of the disease occurred in 9 per cent and miliary dissemination in both lungs in 36 3 per cent Vieta and Craver recorded pulmonary infiltration in 23 8 per cent and multiple isolated nodular involvement in 5 8 percent

Multiple follicular lymphoma also known as Brill Symmers disease was first described by Becker in 1901 Its histologic pattern is characterized by the development of multiple follicle like nodules from the germinal centers of lymph nodes thus the normal morphology of these structures becomes obliterated It has a tendency to penetrate through the capsule of the affected lymph node The disease occurs from infancy to old age, the highest incidence being during the fourth decade Males develop the disease twice as frequently as females The condition may be localized or generalized Superficial lymph nodes are its usual sites of involvement

Gall and his associates observed pulmonary involvement in 2 per cent of their cases On the basis of histologic findings they set up the following classification

Type 1 Tumor consists of homogeneous nodules which are composed of small lymphocytes without the formation of germinal center and without significant number of less mature cells

Type 2 Tumor is characterized by various degrees of germinal center formation The central content of the latter shows cells some of which are primitive stem cells and others with the appearance of clasmatocytes In addition there are lymphocyte like and lymphoblast like cells and mitotic figures The germinal center is surrounded by a collar of mature lymphocytes

Type 3 Lesion differs from the previous ones by the absence of the lymphocyte collar by the predominance of large clasmatocyte like

per cent incidence of positive tuberculin reactors in this group as compared with the anticipated 50 per cent Parker and his associates observed that patients who reacted positively to tuberculoprotein previously failed to show a positive tuberculin reaction when they developed Hodgkin s disease De Marval noted that patients with this disease do not become positive reactors to tuberculin following inoculation with BCG vaccine The converse is true of persons without Hodgkin s disease Another interesting observation is that of Forbus and his collaborators (1942) who found Brucella by culture of either blood or lymph node in nearly 60 per cent of their patients with Hodgkin s disease In none of these patients were Brucella immune bodies demonstrable

Reticulum cell sarcoma so designated because of its characteristic cellular composition, is a very malignant tumor It has varied localization, often, it is generalized On macroscopic examination, it is of somewhat elastic, more or less firm consistency Its cut surface appears grayish white and homogeneous, with discrete and conglomerate nodules or masses Ginsburg (1936) reported a case in which postmortem examination showed reticulum cell sarcoma The neoplasm formed a complete envelop about the right lung Also, there was some pleural involvement on the left side but the lung was not affected

Lymphosarcoma was first separated by Kundrat in 1893 as a special pathologic entity It is encountered in two forms (1) lymphocytic sarcoma, and (2) lymphoblastic sarcoma

According to Jackson it is a diphasic disease as to age It is most common in childhood and in the aged, it is rarely, if ever, seen in the twenties and thirties This neoplasm is of unifocal origin and metastasizes by lymphatic spread Primary pulmonary lymphosarcoma is extremely rare Gannon in 1928 reported a case in a child Pekelis described one which was thoroughly studied on postmortem examination He found a hard nodular yellowish pink mass, the size of a small orange, which occupied the left lower lobe of the lung The mediastinal lymph nodes were not involved but there were metastases to the sternum, the fourth and fifth ribs and the liver Resection of the lower lobe of the right lung was performed for the patient of Spatt and Grayzel Examination of the surgical specimen revealed a tumor which measured 17 by 11 by 3 5 cm, and was proved to be lymphoblastoma Following recovery from the operation the patient enjoyed good health and there was no evidence of metastasis during a 14 months observation period A similar case was recorded by Willis except that the surgically

supervening infection of the lung Dull thoracic pain, substernal or lateral may persist for an extended period of time and become progressively worse It may radiate to the shoulder region The pain is due either to pressure on nerve structures or involvement of the pleura Dysphagia may be complained of when mediastinal tumor masses compress the esophagus Occasionally, thoracic symptoms are accompanied by neurologic manifestations, such as paresthesias, monoplegia or paraplegia These are brought about by pressure of collapsed vertebrae affected by the disease. Also, serious pathologic neurologic changes may result from extradural tumor masses either by pressure or by interference with the normal blood supply of the cord It is well to keep in mind that intense pruritus may precede other symptoms of Hodgkin's disease by months, or even by years

There are a number of associated toxic symptoms These include increased fatigability, which is often the first symptom noticed by the patient, asthenia, weakness, anorexia and weight loss Gradually, it becomes evident that he is the victim of a chronic, apparently obscure illness He will complain of sustained low grade fever or of recurring bouts of high temperature Night sweats, often drenching and exhausting, may be associated with the febrile state

Diagnosis

A careful and complete survey of the patient is the only expedient means in arriving at a correct diagnosis of lymphomatoid diseases We intend to give the details of diagnostic approach with reference to Hodgkin's disease, with brief commentary on allied conditions concerning certain specific points

Fever is common during some phases of Hodgkin's disease, although it may be low or absent in old persons Ordinarily, fever may reach 100° to 101° F Terminally, it rises to 105° F Not infrequently, the pulse rate is higher than would correspond to the elevated temperature In a great many instances, one finds periodically, rather regularly recurring alternating cycles of febrile state The temperature which is of remittent type, gradually rises in about three to five days to 103° F It stays on this level for about five days, then it gradually returns to normal in a few days The ensuing afebrile period lasts from 10 to 14 days and is followed by a repetition of the cycle This peculiar type of febrile reaction is recognized as significant in the diagnosis of Hodgkin's disease although it is admitted that it occurs during certain phases of

cells resembling those seen in reticulum cell sarcoma, by the presence of giant cells similar to Greenfield cells, and by the larger size of the follicles with a limited tendency to confluence

Type 4 Tumor is comprised of large, irregular follicles The nodules show evidence of rupture and mixture of follicular and pulp cells

This neoplasm may progressively metamorphose into lymphosarcoma or Hodgkin's disease *Jackson observed* such occurrence in 60 per cent of his cases Regardless of its location, follicular lymphoma may be associated with hydrothorax in more than 20 per cent of the instances Hepatomegaly occurs in about 10 per cent and splenomegaly from 30 to 60 per cent

Symptoms

It is beyond the scope of this discussion to deal with the symptoms *of lymphomatoid diseases in general* They are varied and a great many, depending upon the part of the body or system involved We wish to refer, however, to clinical manifestations caused by these tumors with mediastino pulmonary and pleural involvement

On account of the relatively high incidence of Hodgkin's disease this condition deserves special attention Some or all of its localizing symptoms may occur in patients with other types of lymphomatoid tumors

The onset of Hodgkin's disease is insidious The patient may complain of unproductive, sometimes distressing cough of several weeks' or months' duration Gradually, the cough becomes productive of mucoid or mucopurulent expectoration Pulmonary hemorrhage may be the presenting symptom It is more common to see patients in whom cough persisted for some time prior to the appearance of hemorrhage Blood-streaked sputum may persist for months In other instances, pulmonary hemorrhage is profuse and recurrent Hemorrhage originates from intrabronchial granulation, polyp formation or from central necrosis in the tumor mass, which erodes a blood vessel and the adjacent bronchus In *a small percentage of the cases,* hoarseness develops as the result of involvement of the recurrent laryngeal nerve by a mediastinal tumor mass Asthma like wheezing may occur from stenosis of one of the large bronchi or trachea brought about by pressure or penetration by tumor masses The severity of dyspnea is determined by the extent of pulmonary disease, amount of pleural effusion, compression of vital structures by mediastinal masses of the *neoplasm and by the presence or absence of*

longed arm to-tongue circulation time Angiocardiography is the best method for ascertaining the site of circulatory obstruction

Histologic examination of enlarged lymph nodes is the best means for establishing a definite diagnosis It is well to bear in mind that not all coexistent enlarged lymph nodes show characteristic pathologic alterations For this reason when there is reasonable suspicion of Hodgkin s disease—the same holds true of other types of lymphomatoid diseases—and the examination of one lymph node reveals no confirmatory evidence another lymph node should be removed for microscopic inspection As to taking a biopsy specimen Jackson s advice is well worth remembering He says

Small satellite nodes rarely show the lesion in question They should be avoided Do not cut through a node in order to remove a portion Nine times out of ten all will go well the tenth time it will grow out into the incision like a courageous mushroom and the patient will be a doctor s daughter

In 1933 Gordon introduced a test presumably diagnostic of Hodgkin s disease The test consists of the injection of a broth suspension of triturated biopsy material from a lymph node into the brain of rabbits or guinea pigs From two to six days after injection impairment of locomotion sets in and it is followed by progressive spastic paralysis These changes are brought about by some encephalitogenic factor The test is positive in from 55 to 75 per cent of the cases with Hodgkin s disease The latter therefore cannot be ruled out on the basis of a negative test Another weakness of the test is that it is not specific that is a positive test occurs in other diseases Further scrutiny of the problem revealed that the positive outcome of the test is attributable to leucocytes particularly eosinophilic leucocytes

All this being so it is better to concentrate on trying to prove the diagnosis by biopsy It is important to resort to obtaining specimens from the skin for microscopic examination when lesions are present which suggest mycosis fungoides

Examination of aspirated bone marrow specimen (from the sternum the spinous processes of the lumbar vertebrae or from the iliac crest) is of utmost importance In Hodgkin s disease one finds a shift to the right in the Arneth and Schilling counts of the neutrophile leucocytes Also the latter show marked toxic granulation Moreover there is evidence of monocytosis and increased eosinophilia of the immature myelocytes

some infectious diseases and in other tumors Customarily, the fever is referred to as Pel Ebstein type for the reason that these writers simultaneously but independently described it in one of the medical journals of Vienna in 1887 Rightfully, the credit for this clinical observation belongs to Murchison of London, England for he recorded and reported it in 1870

Symptoms and signs referable to the skin are present in from 30 to 40 per cent of the cases and vary from pruritus to easily recognizable lesions The latter may be noted in the form of diffuse nodular or flat wart like infiltrations which measure from 1 mm to 3 cm in diameter and are raised from 1 to 2 mm above the skin surface Sometimes ulceration or exfoliation is associated with these changes Usually, these skin lesions are referred to as *mycosis fungoides* This condition is encountered not only in Hodgkin's disease but also in lymphosarcomatosis and leukemia Dark pigmentation of the skin (general melanosis) is seen in from 10 to 20 per cent of patients with Hodgkin's disease It resembles that observed in argyrosis and in certain instances of Addison s disease and hyperthyroidism Jaundice occurs in from 3 to 4 per cent of the cases Occasionally, there are symptoms and signs of herpes zoster

Massive mediastinal involvement may be accompanied by signs of obstruction of the superior vena cava If this is the case, there is edema and bluish engorgement of the face and neck together with cyanotic congestion of the oral and pharyngeal mucosa The eyes are prominent and the conjunctiva is congested There are dilated veins in the neck and anterior chest wall signifying a detour of the blood flow through collateral channels from the superior to the inferior vena cava Also one may find edema of the upper part of the chest and the arms Edema in the upper part of the body is brought about by interference with the normal current of blood and lymph Gall and his associates called attention to the possible involvement of the lachrymal glands in multiple follicular lymphoma which results in unilateral exophthalmos

It is mandatory to examine the patient for the presence of enlarged superficial lymph nodes These are more likely to be involved in various regions of the body unilaterally than bilaterally Palpation of the neck often reveals fullness at its base not only in Hodgkin s disease but also in the other lymphomatoid diseases At the same time the patient may mention that he has puffiness around the eyes on arising In patients with superior vena caval syndrome, the venous pressure is elevated in the arm as compared with the lower extremities There may be a pro

some instances It is impossible to identify the disease from the x ray appearance alone Findings characterized by miliary shadows should be differentiated from those seen in a number of other diseases A list of these is given in the chapter on Collagen Diseases of the Lung In the differential diagnosis of solitary round opacities one should rule out conditions with similar x ray appearance as enumerated in the chapter on Pulmonary Adenomatosis The differentiation of ring like shadows has been discussed in the chapter on Metastatic Lung Tumors

In addition to items mentioned under these headings, it may be desirable to rule out other clinical conditions the manifestations of which may simulate Hodgkin s disease These include brucellosis, typhoid fever, subacute bacterial endocarditis, some of the rickettsial and virus diseases, malaria, toxoplasmosis, amebiasis and other infections of the gastrointestinal tract, genito urinary tract infection and Gaucher s disease The latter is frequently associated with enlargement of the superficial lymph nodes Also, it is known that in rare instances of xanthomatosis there may be a huge enlargement of the cervical lymph nodes

It is mandatory to take roentgenograms of the chest in the standard postero-anterior and lateral positions In this manner, a more accurate assaying can be made of the size, shape, extent, location of the new growth and its relation to other intrathoracic structures In addition, if necessary, one can avail himself of information by taking chest films in the oblique position or with the aid of the Bucky diagram, tomograph or kymograph The latter is of value in ascertaining the presence or absence of pulsation of the mediastinal mass Similar observations can be carried out by fluoroscoping the patient This method is useful for separating the shadow of the mediastinal neoplasm from the contour of the heart and aorta Fluoroscopy is also of advantage in ascertaining the presence of obstructive emphysema on the diseased side and whether or not there is paralysis of a hemidiaphragm Obstructive emphysema develops on the involved side as the result of partial bronchial occlusion by the tumor which permits the ingress of air to certain areas of the lung but prevents its egress When large pleural effusion obscures the picture, it should be removed prior to x ray studies In lymphomatoid tumors, pleural effusion has a tendency to rapid recurrence following its removal Angiocardiography is the best means for differentiating mediastinal vascular disease from tumors and also, for detecting occlusion of the superior vena cava

Returning to general physical examination, mention should be made of the fact that the liver and spleen are palpable in about 25 per cent of the cases In *follicular lymphoma*, *Gall* and his associates found hepatomegaly in 10 per cent and splenomegaly in from one third to two thirds of their patients When compression of the spinal cord develops from either bone or epidural involvement, corresponding *neurologic signs* are detectable

Examination of the chest may reveal *impaired or dull percussion* note over limited areas depending upon the site and extent of the lesion Over massive involvement, breath sounds are absent Sonorous rales are audible over one lung when one of the large bronchi is partially obstructed by *either extraneous pressure or penetration of the new* growth into the bronchial lumen Moist rales are heard over areas of the lung which become affected by superimposed infection There is a tendency for the latter to develop when bronchial stenosis secondary to *Hodgkin s disease or the other lymphoid tumors* interferes with normal ventilation and evacuation of some of the lower air passages Massive disease in one lung is likely to lead to compensatory emphysema on the opposite side Presence of pleural effusion is easily detectable It is either unilateral or bilateral *Exploratory thoracocentesis reveals the character* of the pleural fluid Usually, it is yellowish or amber, slightly turbid with a specific gravity of more than 1,015 Cytologic examination shows predominance of monocytes and lymphocytes In about 2 per cent of the cases, chylothorax is found *It is brought about by occlusion of the* thoracic duct by the neoplasm Hydrothorax occurs in about 20 per cent of patients with multiple follicular lymphoma

In connection with the pathologic findings in Hodgkin s disease and allied disorders, an outline of their various types has been given *Need less to emphasize, x ray findings* vary according to the underlying involvement There may be mediastinal widening, unilateral or bilateral enlargement of the hilar shadows, evidence of penetration of the peri hilar lung parenchyma or increase *in the broncho vascular markings signifying spread* of the disease along these structures In some instances miliary shadows are seen widely scattered throughout both lungs or limited to one lobe, in association with other x ray changes on the same side Circular, dense opacities *measuring from 10 to 30 mm in diameter* or larger may be seen in one or both lung fields Solitary round shadow may be the only pulmonary manifestation of the disease Round or irregular large masses occupy the entire area of one or two lobes in

is known, however, that an apparently benign form of Hodgkin's disease may change into a rapidly progressive one The duration of this disease varies from two and a half months to eleven years The prognosis is less favorable in children than in adults Wright reported a case where repeated authentic histologic examinations established the diagnosis, the patient having been treated with x ray irradiation and was followed for 26 years

(4) According to Jackson, 50 per cent of patients with reticulum-cell sarcoma die within one year

(5) Lymphosarcoma is likely to have a fatal termination within three years

(6) Multiple follicular type lymphoma carries a more favorable prognosis, for it is highly radiosensitive It is well to remember that with repeated irradiation, x ray treatment is less efficacious and finally, it may lose its therapeutic influence entirely Of the 25 patients of Symmers, seven developed polymorph-cell sarcoma, in seven associated Hodgkin's disease and in seven lymphatic leukemia were observed subsequently

Treatment

The necessity of prompt and adequate therapeutic intervention can not be overemphasized Even where the type of lymphoid tumor is known to have unfavorable prognosis, one should not omit treatment Some of these patients may unexpectedly show remarkable favorable therapeutic response Effective treatment, though it will not lead to permanent cure, may bring about substantial improvement With the disappearance of disabling symptoms, invalidism is relieved and the patient continues to live in reasonable comfort In some patients full professional or occupational earning capacity is restored for a number of years and women may bear children The following methods are used in treatment

(1) X-ray
(2) Radium
(3) Radioactive phosphorous
(4) Nitrogen mustards
(5) Miscellaneous measures

Treatment of lymphomatoid tumors with x rays has been practiced on the basis that lymphoid tissue is highly radiosensitive In experimental animals, complete lymphatic atrophy and aplasia of the bone marrow

Laboratory findings may serve as informative adjuncts in the clarification of a diagnostic problem The blood count is often normal in any of the lymphomatoid tumors Of course, this statement is made with the qualification that in case of transition into lymphatic leukemia corresponding changes are to be anticipated quantitatively as well as qualitatively Leucopenia is found in some cases of Hodgkin s disease On the other hand, in its advanced cases, the leucocyte count may vary from 30 000 to 40,000 per cubic millimeter Superimposed infection of the respiratory tract is likely to cause leucocytosis Hypochromic anemia is encountered in a number of lymphomatoid diseases Eosinophilia occurs in from 20 to 25 per cent of the cases with Hodgkin s disease It is less common in multiple follicular lymphoma The eosinophile count may run as high as 30 per cent in Hodgkin s disease Major and Leger reported a patient who had a consistently high eosinophilia which at times rose to 99 per cent The low incidence of positive tuberculin reaction has been discussed previously By the electrophoretic method Peterman and her associates found decreased albumin and increased globulin in the plasma of patients with moderately advanced Hodgkin s disease In far advanced cases both of these protein fractions were reduced due to systemic toxicity Similar findings were observed by Nitsche and Cohen According to Craver, the phosphatase level of the blood serum is increased in Hodgkin s disease Schultz reports that heterophile antibody titers have been found within the diagnostic range of 1 56 or over in Hodgkin s disease

All lymphomatoid malignant tumors are invariably fatal The gravity of this gloomy statement should be modified by the following points

(1) The presence of constitutional symptoms does not necessarily imply a rapid downhill course

(2) Although the inherent structural tendency of lymphomatoid tumors greatly influences the course of the disease the most important determinant of its prognosis is the early institution of treatment With this in mind it may be said that chances for improvement are directly proportionate to the promptness with which the disease is discovered One may add that the longer the disease has been present prior to treatment the less favorable the outlook for therapeutic benefits

(3) It has been stated previously that of the various types of Hodgkin s disease paragranuloma is comparatively benign granuloma is more rapidly fatal and Hodgkin s sarcoma has a grave prognosis It

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can be produced by large doses of x-ray Gall and his associates (1941) investigated the susceptibility of various lymphoid tumors and reported the following

Type of Neoplasm	Per cent resistant to x-ray irradiation
(1) Lymphocytic lymphoma	3
(2) Follicular lymphoma	4
(3) Hodgkin's disease	8
(4) Reticulum cell sarcoma	8
(5) Stem-cell lymphoma	12
(6) Hodgkin's sarcoma	20
(7) Lymphoblastic lymphoma	21

A few pertinent points relative to this subject deserve special attention

(1) X-ray treatment should be carried out by experienced radiologists, but at the same time, the patient should be kept under the close and careful observation of the attending physician

(2) The competent management of these patients consists of much more than the application of physical measures Let us not forget that we are dealing with individuals who must be told about the true nature of their disease If so, these persons are under terrific emotional stress and strain They are living under the sword of Damocles in the form of the potential uncertainty of their affliction and are obliged to adapt themselves to the inexorable fatality of it To assist these individuals in their adjustment to the trials and tribulations of the future requires no small art of medical psychology Indeed, blessed are the patients whose physicians are not trying to treat them with machines alone

(3) Constitutional symptoms (fever, malaise, etc) are not contraindications to x ray therapy

(4) Anemia and low platelet count do not interdict x-ray treatment, provided steps are taken to correct this condition When circumstances demand, repeated blood transfusions are given before and during x ray therapy, together with iron medication Blood counts and differential white blood cell counts should be done at frequent intervals Bone marrow studies give a more accurate information than the usual blood studies

(5) X-ray treatment is permissible and justifiable even in cases of generalized disease In such instances, it may prove to be an excellent

palliative means for the alleviation of the patient's distress and suffering

(6) X ray therapy is not incompatible with the simultaneous administration of penicillin or other antibiotics whenever the latter is indicated for controlling superimposed infection of the respiratory tract

(7) In a number of instances repeated courses of x ray irradiation are called for Precise individualization is imperative in this regard Rigid, set treatment schedule has no place in the management of these patients

(8) It is regrettably a known fact, that x rays may lose their therapeutic effectiveness on repeated applications during a prolonged period

(9) It is well to bear in mind the advice of Isaacs, namely, when decrease in the number of red blood cells and platelets is due to crowding of the bone marrow by blast cells x ray treatment is contraindicated

(10) Pulmonary involvement may disappear with the most gratifying rapidity with corresponding relief from respiratory symptoms

(11) Distressing dyspnea cyanosis and other alarming manifestations of superior vena caval syndrome caused by lymphoid neoplasms of the upper mediastinum may be relieved with remarkable promptness

(12) Rarely bronchial occlusion with consequent lobar atelectasis develops after x ray irradiation of a mediastinal tumor mass Fortunately, such event is of transitory nature It can be corrected effectively by bronchoscopic aspiration by the inhalation of a mixture of 5 per cent carbon dioxide and 95 per cent oxygen or by resorting to both of these measures Carbon dioxide inhalations are given through the BLB mask or equivalent for 15 minutes every hour until satisfactory relief is obtained

(13) X ray treatment is most effective when given on consecutive days

(14) Using filtration with 0.5 mm copper and 1 mm aluminum at a focal distance of 50 cm anterior and posterior irradiation is given with single doses of from 150 to 200 r, measured in air, for a total of from 1,200 to 2,000 units for each of the two fields

The use of radium has been championed by a number of radiologists According to the report of Desjardins and Williams, satisfactory results can be anticipated with radium in mediastinal Hodgkin's disease, lymphosarcoma and allied conditions Its biologic effectiveness is based on the experimental observation of its destructive effect upon cells Lymphocytes and related cells are highly susceptible to the action of radium

It is possible to render phosphorus radioactive by a cyclotron Phosphorus so conditioned can be used for therapeutic purposes when given intravenously Kamen administered radioactive phosphorus, P^{32}, for the treatment of *Hodgkin's disease, lymphosarcoma and reticulum cell* sarcoma The results were not as satisfactory as with x ray treatment Kenney and Craver recommended radioactive phosphorus for the treatment of lymphosarcoma either primarily or secondarily (with x ray irradiation) They observed complete remission in four out of their 22 cases, although there was recurrence of the disease in two of them, it was readily controlled by additional treatment In three patients, the disease regressed about 75 per cent and in one patient, 50 per cent Eleven patients had no benefit from subsequent x ray treatment Also, it was noted that remissions lasted longer from radioactive phosphorus than from x ray irradiation They advocate courses of from 70 to 100 micro curies of radioactive phosphorus per kilogram of body weight in divided doses every seven to 14 days Frequent blood counts and bone marrow studies are mandatory during the course of treatment on account of the possible damage to the hematopoietic system

Brues and Jacobson found radioactive phosphorus useful in lymphosarcoma but their therapeutic results were variable in Hodgkin's disease The isotope may be given orally or intravenously They advise the following precautions when the isotope is given by mouth

(1) *For the sake of prompt absorption from the digestive tract,* it should be given before breakfast

(2) Administration of iron compounds, alumina and milk should be avoided during treatment with the isotope so as not to interfere with its absorption

(3) Even with these precautions, the oral dose should be one third greater than that given intravenously Their treatment schedule calls for 1 millicurie once to twice weekly over varying periods, depending upon the therapeutic response

Nitrogen Mustards (beta chloroethyl amines, halogenated alkyl amines) have been found experimentally to possess cytotoxic action The latter *manifests itself in inhibiting mitotic* activity The susceptibility of cells is proportionately increased with their cellular activity Animal experiments as well as clinical observations revealed that their administration resulted *in lymphopenia, granulocytopenia, thrombo*cytopenia and moderate anemia Lymphomatoid tumors are susceptible to the influence of nitrogen mustards It has been shown that under

their effect, transplanted lymphosarcoma in mice disappeared, though recurrence was observed subsequently Two compounds belonging in this group of chemicals are of significance

The bivalent form which is di (beta chloroethyl) methyl amine hydrochloride $CH_3N(CH_2H_4Cl)_2$ and a trivalent form which is tri (beta chloroethyl) amine hydrochloride Both are crystalline and water soluble The former is being extensively used in clinical practice The first patient was treated by Lindskog in New Haven in 1942 At the same time a number of cooperative studies were undertaken The first report on the clinical aspects of the subject was published by Gilman and Phillips in 1946

Goodman and his associates observed encouraging results with nitrogen mustards in Hodgkin s disease lymphosarcoma and leukemia It was noted that even patients who previously became radioresistant showed remission and, what is more their radiosensitiveness was restored In 1948 they reported their results in 13 patients of whom all but four had had previous x ray treatment The therapeutic response was markedly favorable in some of these patients Good results lasted from three weeks to several months In some of the patients the drug unexplainably lost its efficiency Also they found that it was impossible to predict which patients would or would not respond satisfactorily Jacobson and his associates (1946) recorded dramatic improvement with disappearance of fever and malaise in certain patients with lymphomatoid diseases while in others there was no significant remission from the use of nitrogen mustards Similar unpredictability was noted with reference to x ray therapy Some patients who became radioresistant during preceding treatment derived satisfactory improvement from the administration of this drug while others did not Wintrobe and his associates found great individual variations in the therapeutic response to nitrogen mustards as well as in its tolerance In their patients with Hodgkin s disease results were good in 61 per cent fair in 18 per cent and poor in 21 per cent In cases with favorable response fever disappeared dyspnea was relieved hacking cough ameliorated and dysphagia was alleviated In this group, there was definite reduction in the size of mediastinal widening caused by tumor masses and also a recession of the involvement of the lung parenchyma In patients with lymphosarcoma results were good in 36 per cent and poor in 64 per cent They commented on the usefulness of nitrogen mustards where facilities and personnel for x ray treatment are not available Their

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their effect, transplanted lymphosarcoma in mice disappeared, though recurrence was observed subsequently Two compounds belonging in this group of chemicals are of significance

The bivalent form which is di (beta chloroethyl) methyl amine hydrochloride, $CH_3N(CH_2H_4Cl)_2$ and a trivalent form which is tri (beta chloroethyl) amine hydrochloride Both are crystalline and water soluble The former is being extensively used in clinical practice The first patient was treated by Lindskog in New Haven in 1942 At the same time, a number of cooperative studies were undertaken The first report on the clinical aspects of the subject was published by Gilman and Phillips in 1946

Goodman and his associates observed encouraging results with nitrogen mustards in Hodgkin s disease, lymphosarcoma and leukemia It was noted that even patients who previously became radioresistant showed remission and, what is more, their radiosensitiveness was restored In 1948, they reported their results in 13 patients of whom all but four had had previous x ray treatment The therapeutic response was markedly favorable in some of these patients Good results lasted from three weeks to several months In some of the patients, the drug unexplainably lost its efficiency Also, they found that it was impossible to predict which patients would, or would not respond satisfactorily Jacobson and his associates (1946) recorded dramatic improvement with disappearance of fever and malaise in certain patients with lymphomatoid diseases while in others there was no significant remission from the use of nitrogen mustards Similar unpredictability was noted with reference to x ray therapy Some patients who became radioresistant during preceding treatment derived satisfactory improvement from the administration of this drug while others did not Wintrobe and his associates found great individual variations in the therapeutic response to nitrogen mustards as well as in its tolerance In their patients with Hodgkin s disease, results were good in 61 per cent, fair in 18 per cent and poor in 21 per cent In cases with favorable response fever disappeared, dyspnea was relieved, hacking cough ameliorated and dysphagia was alleviated In this group, there was definite reduction in the size of mediastinal widening caused by tumor masses and also, a recession of the involvement of the lung parenchyma In patients with lymphosarcoma results were good in 36 per cent and poor in 64 per cent They commented on the usefulness of nitrogen mustards where facilities and personnel for x ray treatment are not available There

experience coincides with the observations of others who noted that improvement from this treatment may be striking but short lived although in some instances, remission may last from four to 18 months It is emphasized that in spite of the decrease in the subjective and objective manifestations of lymphomatoid diseases the treatment is not curative as far as recovery is concerned but only palliative Craver who is one of *the foremost authorities on this subject warns against the use* of nitrogen mustards in early localized forms of Hodgkin s disease and lymphosarcoma For these conditions adequate x ray irradiation is the *treatment of choice* He says

> Even when Hodgkin s disease or lymphosarcoma begins to generalize, by and large, roentgen irradiation is more effective than any of the nitrogen mustards that have been tried up to the present time

Concerning the technical aspects of treatment with nitrogen mustards, the following items are of importance

(1) Di (beta chloroethyl) methyl amine hydrochloride is preferable to the trivalent form of nitrogen mustard

(2) Its dose is 0 1 mg per kilogram of body weight (2 2 lb)

(3) No single dose should exceed 8 mg

(4) *Injections of the drug are given intravenously on four con*secutive days

(5) The drug is placed in a sterile container and dissolved in *10 cc of sterile isotonic solution of sodium chloride The solution pre*pared should be used within five minutes so as to prevent the transformation of nitrogen mustard by hydrolysis into the ethylene ammonium derivative

(6) The intravenous injection should be given rapidly so as to assure painlessness and obviate subsequent local phlebothrombosis It is expedient to use an intravenous needle with an attached rubber tube through which isotonic solution of sodium chloride or 5 per cent dextrose is delivered

(7) *The skin of the patient physician and nurse must be scrupu*lously protected from getting in contact with the drug

(8) General toxic symptoms, such as nausea and vomiting are to be anticipated Some patients develop diarrhea following injections Nausea and vomiting usually appear within one to three hours after the first few injections and persist for about three to four hours Vomiting can be prevented by the administration of sedative doses of one of the

barbiturates, and by giving the injections before the patient has eaten

(9) On account of the depressive effect of nitrogen mustards upon the hematopoietic system repeated examinations of the blood are mandatory during treatment As pointed out by Jacobson and his associates, the following hematologic changes can be expected

(A) Lymphocytopenia after the first injection which is bound to become progressively worse for from six to eight days There is a tendency to return to normal levels between two to three weeks, somtimes longer

(B) The monocytes behave in a similar manner

(C) Severe neutropenia takes place with recovery usually within two weeks after the maximum depression

(D) Marked thrombocytopenia during the third week This may be associated with purpura bleeding from the gums and delayed clot reaction

(E) Fall in the number of red blood cells and in the amount of hemoglobin within the first two weeks after treatment

(F) There is a decrease in the number of reticulocytes within a week after the first injection

(10) Repeated courses may be necessary in some instances

(11) Treatment with nitrogen mustards may be combined with x ray therapy According to the experience of Jacobson simultaneous treatment with nitrogen mustard and x ray is quite efficacious however alternating these two methods is not more effective than treatment with one or the other alone He reported similar experience with simultaneous administration of nitrogen mustard and radioactive phosphorus Gellhorn and Collins found in a large group of patients that the length of x ray therapy could be reduced by one half with the administration of nitrogen mustards They noted however that the addition of nitrogen mustards to x ray therapy did not modify the duration of the disease or the life expectancy of the patient

Miscellaneous Measures include some of the oldest and some of the newest therapeutic attempts Among the former mention should be made of general supportive and symptomatic treatment As far as circumstances permit attempts should be made to restore the patient's general condition as near the normal level as possible At the same time, realizing the gravity of the situation no effort must be spared in offering the patient all available means for symptomatic relief

Temporary regression of the new growth was noted by several clin

icians in patients with Hodgkin's disease and lymphosarcoma following treatment with *adrenocorticotropic hormone* (*ACTH*) and cortisone

Aureomycin was found ineffective in five patients reported by Goldman, whereas three of four patients given nitrogen mustard had prompt, complete, but temporary, remissions Cortisone administered to 10 patients by Jacobson and his associates produced considerable improvement in seven, the remaining three died, but death was not due to the drug Whereas the cortisone caused the symptoms to become reversible in part, the basic pathologic process was not affected

Broun and his associates reported remission in Hodgkin's disease treated with colchicine, 1/100 grain three times daily, combined with daily intramuscular injection of desoxycorticosterone, 5 mg and intra venous injection of 1 Gm of ascorbic acid

Karnofsky and his collaborators recorded transient improvement with the use of triethylene melamine (TEM, 2, 4, 6 triethyleneimine s triazine) in Hodgkin's disease and lymphosarcoma They found it effective when given intravenously at a daily dose of 2 to 3 mg for a total dose 5 to 20 mg This drug can be used for oral therapy although it may cause occasional nausea and vomiting By mouth the recommended dose is from 20 to 40 mg given in a three to five week period

For localized extrapulmonary lesions of Hodgkin's disease and lymphosarcoma, surgical removal has been practiced successfully for decades With the advent of modern methods of anesthesia and with recent advances in thoracic surgery, the same principle is applicable to solitary primary manifestations of these conditions in the lung Lobec tomy or pneumonectomy with recovery from primary pulmonary lymphosarcoma was reported by Spatt and Grayzel, Willis, Maier and others Beck and Reganis analyzed six cases found in the literature and studied nine others and concluded that the diagnosis can be made only after the growth has been explored surgically They recommend surgical removal, lobectomy seems adequate if the lesion is small and peripheral

Finally, mention should be made of the much heralded anti reticular cytotoxic serum (A C S) of Bogomolets Skapier who used it in 22 cases expressed the view that though it is not a curative agent, it is a valuable adjunct in the treatment of lymphomatoid diseases He observed hema tologic improvement in the majority of this group, together with improvement in the general condition of the patients Further studies

will be required for the final evaluation of the therapeutic usefulness of this serum

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UNCOMMON TUMORS OF THE LUNG

By ANDREW L BANYAI, M D AND J WINTHROP PEABODY, M D

Customarily, tumors are divided into benign and malignant forms Common and uncommon benign neoplasms of the bronchus are presented in a separate chapter Due space has been given to the discussion of primary bronchogenic cancer on account of its rather high incidence Metastatic malignant tumors and those belonging to lymphomatoid diseases and to diseases of the hemopoietic system are discussed under respective headings Accordingly, this section is limited to a restricted number of subjects

Primary Sarcoma of the Lung

Primary sarcoma of the lung is more often encountered in children and in adolescents than in adults Even so, it is an extremely rare tumor On necropsy its incidence varies from 0 02 to 0 12 per cent The youngest patient on record with this condition is that of Gezelius and his associates They reported on an infant aged three weeks, with dyspnea, cyanosis and fever Post mortem examination revealed a large, lobular sarcoma of the right lower lobe Three types are distinguished, namely the round cell type, small round cell type and the spindle cell type In some instances, classification may be difficult, for various cell forms may be found in different parts of the new growth Such tumors are best designated as mixed cell tumors Sarcoma arises from the supportive tissues of the lung and has a tendency to develop into large masses The latter may replace the entire lung on one side In extremely rare instances, it may closely resemble the appearance of an intrabronchial pedunculated polyp Erosion of the overlying ribs and perforation of the chest wall may take place Pulmonary sarcoma is of firm or soft consistency, its cut surface is white or brownish yellow and may show hemorrhages and evidence of necrosis The latter may result in cavity formation In some instances, extensive calcification is noted Development of bronchial stenosis and occlusion have also been observed In either event, favorable conditions are thus brought about for superimposed infection, bronchiectasis and lung abscess Pleural effusion is infrequent It may be serofibrinous or hemorrhagic Metastasis takes place through the blood stream to many parts of the body The earliest spindle-cell sarcoma of the lung on record was reported by Chiari in 1877

Symptoms of primary pulmonary sarcoma do not differ from those encountered in other (benign or malignant) tumors of the lung

Constitutional manifestations are absent in the early stage of the disease With the development of superimposed pulmonary infection toxic symptoms ensue, such as chilly sensations, moderate high fever, malaise, anorexia and loss of weight

Physical examination may reveal no abnormal changes while the neoplasm is small Large tumors on the other hand are easily located by the presence of diminished chest expansion, dull percussion note, absent breath sounds and decreased voice conduction over the corresponding lung Very large sarcomas cause bulging of the hemithorax as if the patient had a very large pleural effusion Bronchial stenosis is suspected when there are unilateral sonorous rales So called moist rales are audible in superimposed infections of the bronchioles and lung parenchyma

Roentgenologic studies should include films taken with the patient in various positions (postero anterior, lateral and oblique) Advantage should be taken of the value of films taken with the Bucky diaphragm and also of tomograms Adjunct roentgenologic methods are discussed in connection with metastatic tumors of the lung Also additional pertinent diagnostic measures are presented in the same chapter X ray films show sarcoma of the lung in the form of a round or oval, sharply demarcated, homogeneous dense shadow It may be localized in the apical or subapical region or in the middle or lower one third of the lung field Some of these tumors occupy the entire area of one or more lobes Cavity is recognizable in some of these cases in the central area of the new growth Others reveal the presence of calcification within the tumor The roentgenologic differential diagnosis is given in the chapter on Pulmonary Adenomatosis Extensive atelectasis is associated with characteristic x ray findings The latter are outlined in detail in the chapter on Atelectasis

Bronchoscopy is of value as a diagnostic aid in two ways

(1) Malignant cells may be found in the bronchoscopically aspirated secretions Hematoxylin eosin, Wright stain, the Dudgeon or Papanicolaou method can be used for staining the specimen Technical details are described in the chapter on Primary Bronchogenic Carcinoma We feel that it is not so much the choice of staining technique as the experience and ability of the man behind the microscope that counts the utmost in this matter

(2) In exceptional cases, bronchoscopy may reveal an intra bronchial polypoid neoplasm In such cases it is mandatory to take a biopsy specimen Such instances were reported by Herrnheiser and by Baum and his associates

Prognosis

The prognosis of primary sarcoma of the lung is unfavorable unless the condition is diagnosed early and immediate steps are taken for effective treatment Without adequate therapeutic intervention pul monary sarcoma has fatal termination in from two to 32 months

Treatment

When the tumor is situated in one lobe or it is limited to one lung surgical intervention in the form of resection, is the treatment of choice provided there are no metastases and other conditions do not contra indicate operation Lobectomy or pneumonectomy is done depending upon given circumstances of the individual Davis reported on a case of primary sarcoma of the lung treated by lobectomy In experienced hands operation mortality after lobectomy is less than 0 5 per cent

Sarcoma is a highly radiosensitive tumor Beneficial results from x ray irradiation have been recorded

Intrabronchial implantation of radium needles may bring about improvement in the patient s symptoms Edwards in 1934, devised self retaining containers These are small tubes with delicate metal springs which hold the container at any desired location in the bronchial lumen The containers are inserted through a bronchoscope by means of a special introducer The spring can be withdrawn almost completely into the lumen of the container before introduction and withdrawal A long thread is affixed to the upper end of the container and is fixed to the cheek The container holds from eight to 16 radon seeds, each of which is 1.5 millicurie strength The seeds are surrounded by 0 3 mm screens of platinum The latter cuts off practically all beta rays which are known to have a cauterizing effect Edwards recommends that the containers should be retained by the patient for seven days so that the mass of the tumor receives approximately 1 800 milligram hours of radium

Nitrogen mustards have been found to exert impressive therapeutic influence upon some of the lymphomatoid neoplasms Detailed discus sion of the mechanics of their action and the technique of administration are presented in the chapter on Lymphomatoid Diseases of the Lung

Craver (1948) used this drug in treating miscellaneous cases of sarcom but observed slight or moderate palliative effect only

In addition to attempts at direct therapeutic approach, a numl of other measures may be necessary for the alleviation of the patie symptoms In rare instances, it may be possible to remove part of the tumor which is protruding into the bronchial lumen Clearing the air passages in this manner is likely to eliminate atelectasis distal to the bronchial obstruction and thus relieve dyspnea Supportive measures may greatly improve the patient s general physical condition and his psyche It is mandatory to use adequate doses of drugs for the control of cough and relief of pain Superimposed infections are treated with penicillin by inhalation, or given intramuscularly In some instances administration of streptomycin, other antibiotics or sulfonamides may be necessary

Primary Malignant Hemangioma

This tumor of the lung was first reported by Wollstein in 1931 The neoplasm was localized in the right lung which showed a fleshy consis tency On microscopic examination, it was found composed of masses of capillary blood vessels with a lining of a single layer of endothelial cells Some areas of the tumor were less vascular and revealed slit like alveoli and bronchioles In others, only solid tumor tissue was seen without alveoli There was a definite progression of the neoplasm through the alveolar septa causing thickening of the latter and also, obliteration of the alveoli

Primary Leiomyosarcoma

Primary leiomyosarcoma of the bronchus originates from the smooth muscles of this structure The number of recorded cases is very small Randall and Blades reported an instance where the tumor measured 10 x 14 cm In the roentgenogram, it occupied the hilar region and was associated with elevation of the corresponding hemidiaphragm and with displacement of the mediastinum

An exceedingly rare case of *chondrosarcoma* confined to the pul monary artery and its branches was recorded by Lowell and Tuhy

Primary Rhabdomyosarcoma

Primary rhabdomyosarcoma of the lung is very rare Presumably, it arises from a pulmonary embryonal structural disturbance Helbing is credited as being the first to report an instance His case, however, as well as that of Zipkin showed predominant teratomatous characteristics

Clinical and necropsy reports are available on an unmixed form of rhabdomyosarcoma recorded by McDonald and Heather Their patient was a man aged 52 years who was first seen on account of cough, dyspnea and pain in the right hemithorax At this time, his condition was diagnosed as right apical tuberculosis and left spontaneous pneumothorax Two months later, the patient was seen again, with exaggerated symptoms which were aggravated by pulmonary hemorrhage Examination revealed a circumscribed lesion in the right lung, together with clubbing of the digits Rapid downhill course and death followed Necropsy showed bilateral small pleural effusion There was an irregularly lobulated tumor in the right lung The cut surface of the new growth was yellowish white, with many areas of necrosis and hemorrhages Also, the right tracheobronchial lymph nodes were involved and there was an invasion of the pulmonary vein, left auricle of the heart and the mitral orifice There was an old fibrocaseous tuberculous focus in the apex of the right lung Histologic sections showed a highly pleomorphic pattern with small anaplastic cells spindle cells of varying length often in parallel bundles There was a well marked longitudinal striation Masses of tumor cells were irregularly intersected by coarse collagenous strands Cowdrey (1947) states that rhabdomyosarcoma responds favorably to treatment with nitrogen mustards

Myoma of the Lung

Myoma of the lung is very rare Recently, Sherman and Malone reported four cases They noted that the tumors were single, spherical, firm on palpation, measuring from 2 5 to 8 cm in diameter and showed opaque, white, interlacing whorls on the cut surface Roentgenologically, myoma appears as a homogeneous, dense, well demarcated round shadow Also, these authors point out that both benign and malignant muscle tumors of the lung may become enlarged over a period of six to 12 months

Teratomas of the Lung

Teratomas of the lung belong in the category of extremely rare primary neoplasms of this organ As far as their site is concerned, these tumors are customarily associated with the mediastinum Cases are on record, in which mediastinal teratomas, that became malignant, formed extensive metastasis in the lung Primary pulmonary teratomas are solitary, spherical, fluctuating structures Sometimes they have a fleshy consistency Their size varies from pigeon s egg to that of grape fruit

or coconut The surface is smooth, somewhat lobulated The cross section reveals many cystic spaces or a material of friable consistency, with intersecting fibrous strands The contents of the cystic variety are watery, syrupy or gelatinous The color of the contents may be milky yellow, light or dark brown It may or may not communicate with an adjacent bronchus Its wall varies from 2 mm to 2 cm in thickness On the inner surface of the wall, there may be a number of pedunculated protrusions, measuring from 1 to 4 cm in width Also, often there are small nodular structures covered with lanugo The term teratoma is derived from the Greek word, tres, which means three This refers to the composition of this tumor, which consists of the derivatives of the three embryonic germinal layers, the ectoderm, mesoderm and endoderm Gross and microscopic examinations reveal, with great variations the following findings

(1) Ectodermal derivatives Skin and its appendages, including hair, nerve cells and teeth

(2) Mesodermal derivatives Masses of striated or smooth muscles adipose tissue, blood vessels, cartilage, with or without bone formation and hemopoietic tissue

(3) Endodermal derivatives Pancreatic tissue, small masses of thymus, thyroid, organoid structures resembling bronchi intestine and others

The great majority of teratomas are seen in the first three decades of life For a great many years they may exist symptomless They may remain of the same size for an extended period of time Symptoms develop because either there is pressure on the surrounding organs or infection takes place through the communicating bronchus Pressure symptoms are brought about by rapid enlargement of the teratoma Just why benign tumors, which are stationary for years, begin to grow and expand rapidly, *has not been solved as yet Similar uncertainty* prevails concerning the question of why some of these benign tumors metamorphose into malignant ones The fact is that all teratomas are potentially malignant Transformation into a malignant neoplasm, of course, implies aggressive tendencies as far as neighboring structures are concerned and also metastasis, particularly to the liver, but also to other organs

Chondroma

Chondroma of the lung parenchyma is a very rare benign tumor *It* consists of hyalin and fibrocartilaginous tissue, with or without foci of

calcification and ossification Its size varies from less than one centimeter to 20 centimeters in diameter With rare exceptions, it is visualized in the roentgenogram as a solitary new growth It casts a round or oval, sharply demarcated, dense shadow

Hamartoma

Hamartoma is a slow growing, mixed benign tumor It consists predominantly of cartilaginous new growth Also, it contains other tissue elements of the lung *The term coined by Albrecht in 1904 is derived* from a Greek word which means "to fail", "to err The tumor is sharply delineated, it shows a lobulated contour firm consistency and various stages of ossification Its size varies from a few millimeters to 15 centimeters or more in diameter Small and medium sized hamartomas are usually found subpleurally, either in the lateral parts of the lung near the diaphragm or interlobar fissure Roentgenograms taken in the postero anterior and lateral positions reveal the neoplasm as a circumscribed dense, slightly lobulated, round shadow, possibly with scattered or confluent areas of increased density suggestive of ossification

Osteochondrosarcoma

Osteochondrosarcoma with primary localization in the lung was observed by Greenspan in 1933

Hamartoma Osteochondromatosum Pulmonis Malignum

This term was applied by Simon and Ballon to an unusually large hamartoma of the lung The tumor, which occupied the entire area of the left lower lobe was found in a man aged 49 years Roentgenologically, a sharply demarcated, slightly lobulated, dense mass was seen in the middle and lower one third of the hemithorax Necropsy revealed a roughly oval, lobulated, solid neoplasm which showed bony firmness in some places while elsewhere it had a cartilaginous or fleshy consistency On microscopic examination, it was noted that there were characteristics of every stage of bone formation, also, there was evidence of invasion of the mediastinal fat and the lung parenchyma

Primary Malignant Melanoma

Primary malignant melanoma of the lung with involvement of the hilar lymph nodes was diagnosed in one of the patients of Carlucci and Schleussner The condition was treated by total pneumonectomy

Neurogenic Sarcoma

Primary neurogenic sarcoma of the lung was removed by lobectomy by Meade and his associates (1947)

Mixed Bronchogenic Carcinoma and Sarcoma

This tumor was diagnosed on microscopic examination in one of the patients of Graham and Womack in 1945 Cough of several years' duration and severe paroxysmal cough of a few months' duration preceded total pneumonectomy in this man, aged 51 years Inasmuch as the histologic findings were so unique, we quote them verbatim

"On microscopic examination sections showed an extremely bizarre malignant tumor of the lung in which both epithelial and connective tissue elements were taking part Elongated cords and islands of malignant epithelial cells could be seen growing within a fibrous tissue stroma The epithelial cells were extremely anaplastic, rapidly growing with numerous mitotic figures The individual cells were variable in size, shape and staining reaction In many areas central degeneration could be seen with debris resembling keratin within the degenerated areas The stroma was the most remarkable part of the tumor It was extremely cellular, the individual cells were spindle shaped and the nuclei showed evidence of rapid growth with numerous mitotic figures With the Masson stain, these cells could be seen actively laying down collagen and were definitely fibroblastic in origin"

Kaposi's Disease

(Angioreticuloendothelioma or Disseminated Visceral Idiopathic Hemorrhagic Sarcoma)

The disease entity bearing the name of Kaposi, is characterized by multiple hemorrhagic sarcomas of the skin Since the time of its first identification in 1872, it has been recognized that lymph nodes and internal organs may be involved by the same pathologic changes As a matter of fact, in some instances, visceral involvement may precede skin lesions Also, a few cases have been reported by Choisser and Ramsey, by Weller and by Nesbitt and his associates in which Kaposi's disease with visceral involvement was seen without skin lesions Kaposi s disease occurs almost always in the male, usually during the fifth, sixth or seventh decade of life According to Doerffel, less than one per cent of cases occurs during the first decade Sarcoma of Kaposi consists of

connective tissue and endothelial elements of thin walled, dilated vascular spaces (hemangiomas) At the onset, the neoplasm is benign in character but subsequently, it becomes malignant When internal organs are involved, the tumors are usually multicentric in origin rather than metastatic Lesions of the skin appear in the form of bluish purple, soft, fluctuating nodules varying in size from that of a split pea to one inch in diameter In other instances, yellowish blue, cord like indurated masses are found on the trunk and extremities, some of them running parallel to large blood vessels The consistency and color of the individual lesion is dependent upon the predominance of vascular or connective tissue elements (fibroblasts) At times, the sarcoma is found in the form of violaceous plaques Transformations from predominantly vascular to predominantly fibrous tumor is not uncommon Edema of an extremity may result from interference with the flow of lymph and with the venous return by fibrous cords

In order of descending frequency, the following sites are known as favorite locations of Kaposi s sarcoma skin, prepuce and glans penis, submucosa of the gastro-intestinal tract, upper and lower respiratory tracts (larynx trachea, bronchi lung parenchyma) superficial and deep lymph nodes and pleura Other possible sites are the pericardium, peritoneum, spleen, liver, pancreas, suprarenal gland, pituitary gland, kidneys, bladder, testicles, peripheral arteries and veins, epiphysis, diaphysis, marrow and periosteum of bones, muscles, particularly the diaphragm and rarely the myocardium

Stats reported on two patients in whom pulmonary involvement with Kaposi s sarcoma was found together with similar changes in the hilar lymph nodes and in the pleura and also, with pleural effusion The latter is either straw colored or serosangineous In his report, Stats recorded the following pathologic findings

> "The pleural surfaces of the lungs were studded by irregular, flat hemorrhagic plaques which penetrated the pulmonary parenchyma in some places In addition, several discrete nodules were present in the right upper and left lower lobes At the hilus of each lung there was a marked condensation and increase in firm, hemorrhagic neoplastic tissue which invaded both lower lobes This encased the vessels and the bronchi on the one hand and was continuous centripetally with similar tissues in the posterior mediastinum on the other'

Also Denzer and Leopold recorded the case of a four and one half year

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3 *Another unusual instance of pulmonary neoplasm is represented* by benign metastasizing thyroid tumors the first of which was reported by Cohnheim in 1876 In his case, necropsy showed a moderately en larged thyroid gland without *histologic evidence of malignancy,* also there were metastatic nodules in the lungs and bronchial lymph nodes in addition to similar foci in the lumbar vertebrae, the sacral and iliac bones Microscopic examination of these metastatic tumors revealed findings characteristic of simple colloidal goiter Thorek and Thorek re *corded the case of a 33 year old woman in whom bilateral, widespread* pulmonary metastasis from thyroid adenoma was observed during a 15 year period This patient had four operations for recurrence of thyroid growth following her first operation for goiter at the age of 18 years In this connection they refer to other instances where hyperplastic colloid *goiters gave rise to either benign or malignant metastasis in various* organs and tissues without any structural change in the goiter itself Such goiters are considered histologically benign but clinically malignant The metastasis is facilitated by the abundant vascularity of the thyroid Me tastatic foci may remain dormant and symptomless for many years, as in the case reported by Thorek and Thorek, or may manifest malignant tendencies even when they originated from benign primary adenoma Without wishing to detract anything of the value of these observations it is well to point out that Willis refers to these tumors as colloid contain ing vesicular adenocarcinomas which closely resemble normal thyroid or colloid goiter

4 *Adenoacanthoma of the uterus* is actually a form of carcinoma *of the endometrium, in which squamous cell epithelium is found* It can metastasize to the lung

5 *Arrhenoblastoma* is a term first introduced by Meyer (1931) It is an unusual ovarian tumor associated with masculinization It occurs in women between the ages of 20 and 40 years Few instances are on record where the disease was observed in adolescents and in the aged Clinically, these tumors have been encountered in various sizes They are of solid consistency, *homogeneous or cystic On histologic examination* the structure of tubular glandular tissue is seen Norris reported a case with pulmonary metastasis in addition to other widespread metastatic foci

6 *Chloroma* is a tumor of myeloblastic origin, which, in the opinion of Willis, is but a variant of myelogenous leukemic metastasis or infiltra tion It is seen in children and young adults Roehm and his associates

described their findings recorded on postmortem examination of a 13 year old girl The neoplasm involved the periosteum of the skull, ribs, sternum and vertebral bodies, the lungs, and several other organs and structures The lungs were found nodular on palpation The cut surface presented a bizarre appearance, with numerous reddish purple and a few green, slightly elevated areas which measured up to 2 cm in diameter The peribronchial lymph nodes were olive green in color and varid in size up to 1 cm in diameter Microscopic examination revealed the following

> " the tumor cells were round or oval averaging from 9 to 12 microns The nucleus was placed acentrically at the edge of the cell and showed a rather lightly staining chromatin material without radial distribution of the granules The cytoplasm was quite plentiful and clear '

In their commentary, Roehm and his associates point out that chloroma is an incorrect term for the green coloration (the Greek word "chloros means green) is not specific of any one tumor cell type Actually, the green discoloration of the tumor tissue is due to phagocytization of blood pigment in obstructed capillaries by endothelial cells The tumor cells themselves are not directly responsible for the green pigmentation of the tumor Doub and Hartman (1935) reported a case in which there was extensive infiltration of the right lung together with pleural effusion on the same side Also the patient had marked exophthalmos, masses over the skull, edema of the upper lids, generalized lymph node enlargement and enlargement of the lower end of the humerus The diagnosis was corroborated by lymph node biopsy

7 *Chondrosarcoma* with metastasis to the lung was recorded by Fry and Shattock, Kosa, Wachner and others The tumor occurs during early adult life and in middle-aged persons Usually it arises from the long bones of the extremities, pelvic bones, or from the ribs Its histologic characteristics are malignant cellular changes with atypical, mitotic cells, with or without the presence of cartilage

8 *Chordoma* is a neoplasm which is derived from embryonic remnants of notochordal tissue in the skull adjacent to the sella turcica, in the sacroiliac region and rarely at certain sites of the spine It can occur at any age Willis who studied five cases of chordoma, describes them as slowly growing, lobulated tumors composed of soft gelatinous tissue, with areas of hemorrhage, cystic degeneration or calcification Microscopic inspection of sections shows markedly vacuolated cells with many poly-

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teratomas) composed of mixture of tissues which show various types and degrees of differentiation Malignant tumors of the testicles have their highest incidence between 20 and 40 years of age They possess a marked tendency to metastasis The latter may develop before or after adequate treatment of the involved testicle Localization of the metastasis is common in the lung Pendergrass and his associates found roentgenologic evidence of mediastinopulmonary metastasis in 54 per cent of their cases Zerman reported a case with pulmonary metastasis 11½ years after orchidectomy Effler and Blades performed a left lower lobe resection in a 26 year old patient for solitary metastatic teratocarcinoma with chorionepithelioma component Previously no change in the tumor was observed following massive x ray irradiation The metastasis in the lung was first noted one and a half years after the patient complained of enlargement of the left testicle and one year after orchidectomy Interestingly pulmonary metastasis developed in spite of radical lymph node dissection carried out for the removal of the left iliac and retroperitoneal nodes After recovery from the surgical intervention heavy x ray irradiation was administered to the remaining retroperitoneal lymph nodes

13 *Ewing s tumor* is a malignant neoplasm that was first identified in 1922 Ewing originally referred to it as ' solitary diffuse endothelioma on account of the close relationship of tumor cells to blood vessels Also the term ' endothelial myeloma was used for designating it Heublein and his associates consider it a nonosteogenic embryonal osteoblastoma " The usual site of involvement is the shaft of long bones in the following decreasing order of their frequency tibia fibula humerus ulna femur Other possible sites are the spine skeletal structures of the thorax skull pelvis and tarsal bones Multiple bone lesions may be either due to metastasis or simultaneous multiple origin Pathologic fractures are rare The adjacent joints are not involved The regional lymph nodes are enlarged in advanced cases From 20 to 40 per cent of malignant neoplasms of the bone are Ewing s tumors Metastasis to the lung is common and may occur any time during the course of the disease As a matter of fact unless adequate therapeutic intervention is carried out early, metastasis may be found in the lung several months after amputation of the involved extremity The tumor is soft, grayish white and resembles gran

ulation tissue It spreads rapidly through the haversian channels causing a destruction of the normal osseous pattern There may or may not be a secondary reaction on the part of the overlying periosteum The microscopic findings are summarized by Heublein and his associates as follows

"Basically the tumor consists of solid cords of cells separated by fibrous bands, thick or thin Delicate reticulin fibers may exist between individual tumor cells or may be absent The cells generally are rounded unless closely packed, then are polygonal The size is two to four times that of a small lymphocyte The nuclei are rounded and the cell outline is indistinct Often capillary blood vessels occur, either in septa or lying among the tumor cells Certain features of the histopathology of the disease deserve special emphasis and may provide a basis for classification These are

1 The lack of intercellular matrix
2 The rudimentary cell type with slight if any differentiation toward a spindle cell
3 The remarkable uniformity of the tumor cells both in the primary lesion and in the metastases
4 The lack of marked anaplasia histopathologically despite the obvious malignancy of the disease
5 The striking morphologic similarity between tumor cells and the cells of normal embryonal tissues in an exceedingly primitive stage of development, i e, before the determination of cartilage, muscle and other specific tissues from the undifferentiated mesoderm Because of the constant association of this tumor with a bone locale, it seems necessary to relate this tumor in some manner to osteogenic mesenchyme

As a sidelight on the controversy which still prevails concerning the origin and classification of this neoplasm, we cannot refrain from mentioning the thorough-going and highly competent pertinent studies of Willis He refers to Ewing's tumor as a syndrome of nonosteogenic round celled, radio-sensitive tumor of bone, but categorically refutes it as an independent pathologic entity He asserts that Ewing's syndrome may be caused by several different kinds of tumors For the sake of clarification of terminology, he also points out that "Ewing's sarcoma is a misnomer and should not be applied to reticulum-cell sarcoma of the bone

14 *Granulosa cell tumors* originate from normal follicular tissue or

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from the undifferentiated stroma of the ovaries They are seen as white or yellowish solid neoplasms which may be discovered *clinically while* their size is still small, lump like or when they attain excessive growth Histologically they present a picture similar to normal membrana granulosa of the graafian follicle, with *Call* Exner rosettes (*Willis, 1948*) Pulmonary hemorrhage due to metastatic granulosa cell tumor was reported by Freedlander and Greenfield Mandeville s patient, a 40 year old white woman, was hospitalized on account of pain in the chest and dyspnea She had an oophorectomy six years previously An enormous tumor mass was visualized in the lower, posterior part of the left hemithorax The tumor removed by left pneumonectomy measured 15 cm in diameter and proved to be a granulosa cell tumor on microscopic *examination*

15 *Grape like sarcomas* (angioblastic sarcoma) of the vagina of children is a very rare tumor seen only in young, mostly very young children Willis gives the following very characteristic description

> "The bulk of the growth usually consists of a mixture of edematous or myxoma like tissue and more cellular spindle celled and pleomorphic celled sarcoma, scattered through which there may be a few or many cells with cross striation Some of these tumors are highly vascular Metastasis in the lung was recorded by Dugge and Nagel

16 *Nonmalignant metastasizing hemangioma* was first classified as such by *Shennan (1914 1915), although it was first identified* and described by Langhans in 1897 The condition has also been referred to as malignant hemangioma, diffuse hemangioma, obliterating angioma and teleangiectatic splenomegaly It is thought that an angioma may lie dormant for an extended period of time only to go through malignant metaplasia later on and then metastasize A typical case in point was reported by Abrams His patient was a 39 year old white man in whom *postmortem examination showed the following* findings Between the adherent visceral and parietal pleurae there were many multiloculated cysts from 1 mm to 1 cm in size, containing hemorrhagic and greenish yellow coagulated substance The right lung contained a 4 cm lobulated mass with numerous yellowish caseous looking areas Beyond it, there were many cysts, mostly near or around blood vessels, from 1 mm to 1 5 cm in diameter They were blood tinged or contained organized thrombi or clear, yellow, mucoid material Two large cysts were in the interlobar fissure between the right upper and middle lobes The medias

tinal and bronchial lymph nodes showed the same cystic involvement Microscopically, the small cysts were identified as hemangiomas with definite endothelial lining Bone formation with marrow in it was noted in one area Identical lesions were found in the spleen, liver, kidneys and several other structures

There are authoritative opinions which question the existence of this condition as a separate clinical and pathologic entity

17 *Hemangioendothelioma* is a malignant vascular tumor, the main characteristics of which are

(1) It consist of delicate, frequently anastomosing tubular structures that can be identified as immature blood vessels, in addition, there are some fully developed blood vessels and capillaries,

(2) The vascular channels are lined with one or several layers of atypical cells showing signs of malignant metaplasia, such as anisocytosis, polymorphism and hyperchromia, these cells may show abundant proliferation with a resulting occlusion of the primitive blood vessels,

(3) The vascular channels are imbedded in a matrix which contains reticulin fibers and occasionally, large groups of proliferating endothelial cells The extreme rarity of hemangioendothelioma is attested by the report of Drucker He relates that there were only eight pathologically confirmed cases observed at Bellevue Hospital of New York City out of many thousands of patients treated there during a period of 22 years (1925 to 1946) Hewer and Kemp recorded a case in which postmortem examination revealed primary hemangioendothelioma in the right auricle of the heart From here the tumor metastasized to the lungs, bronchial lymph nodes, mesentery, vertebrae and skull

18 *Malignant Hepatoma* is a form of cancer of the liver which consists predominently of liver cells This distinction is emphasized in contrast to the histologic structure of adenocarcinoma of the liver of biliary duct type, which is also known as cholangioma Metastasis of malignant hepatoma to the lung is not uncommon

19 *Leiomyosarcoma* of the stomach with extensive metastasis to the lung was observed by Lyons and Schneider Their patient, a white man, aged 41, was admitted to the hospital with complaints of cough, expecto-

ration of grayish sputum, pain over the left hemithorax and loss of about 40 pounds in weight in the preceding three months His disease followed a rapid downhill course Necropsy showed the following pertinent findings There were only a few small nodular masses in the lower lobe of the right lung A huge tumor mass occupied practically the entire extent of the left hemithorax, with a second mass at its base There were scattered tumor nodules in the parenchyma of the left lung The pleura and pericardium were thickened with tumor tissue The diaphragm showed neoplastic infiltration Three ribs were eroded by the tumor The tumor masses in the lung and the primary new growth in the stomach consisted of oval and elongated cells with mitosis and hyperchromatosis, which were arranged in irregular bands and sheets resembling smooth muscles in some areas

The lung is known as a predilectional site for the metatasis of leiomyosarcoma of the uterus Such occurrence has been noted in middle aged and aged persons but only rarely in young individuals Leiomyosarcoma arises either from myomas of the uterus or from its normal smooth muscles

20 *Liposarcoma* occurs mostly in persons of middle or advanced age and it is only rarely seen in children Common sites of its origin are the lower extremities and various abdominal tissues but it may arise from other locations, such as the head, face, neck, arms and others The tumor may originate from normal fat tissue or rarely, from a lipoma In any event, lipoblasts are considered its basic source of origin According to Stout (1944) the following types of this tumor are encountered

(1) Well differentiated myxoid type
(2) Poorly differentiated myxoid type
(3) Round cell or adenoid type
(4) Mixed forms

The histologic picture is best studied with the aid of special fat stains Grossly, the tumor is encapsulated yellowish brown, and is of firm consistency It may exist without symptoms for many years In some instances however, its course is rapid A number of cases are on record with metastasis in the lung McCormick reports the case of a white woman, aged 35 years for whom an operation was performed six years previously for the removal of a mass in the left arm which measured 9 by 9 by 7 cm Local x ray irradiation was applied in therapeutic doses before and after the operation in addition to implantation of radium postoperatively In spite of these measures, recurrence of the tumor at its original site was discovered three and a half years after operation Sub

sequently, she developed pain in the left hemithorax, lost ground rapidly and died Necropsy revealed straw-colored pleural effusion on the left side and a tumor mass of liposarcoma which occupied the left lower lobe and measured 28 by 22 by 15 cm Effler and Blades cite Flick s patient who complained of pulmonary hemorrhage of six weeks duration and for whom a lobectomy was performed on account of the metastatic liposarcoma of the right middle lobe In this instance, eight years elapsed between the removal of a liposarcoma from the patient's left thigh and the clinical manifestations of pulmonary metastasis

21 *Lymphomatoid tumors* of the lung are discussed in a separate chapter

22 *Melanoma* is a pigmented tumor which is encountered very rarely This is a fortunate situation, indeed, considering that innumerable people have pigmented moles from which most of these neoplasms develop Specific cells, designated by Ribbert as chromatophores are the source of origin of these tumors The latter occur at all ages but are rare in Negroes Their most frequent sites of appearance are the face, neck and the back It is thought that metamorphosis of ordinary pigmented moles into melanomas may take place spontaneously, or it may follow trauma or inadequate surgical intervention for their removal When metastasis occurs, the lung is often involved, in addition to other possible visceral regions

An interesting case of metastatic melanoma was reported by Mandeville His patient, a white man, aged 35 years, had a small malignant melanoma removed from the left shoulder region Four years later, a solitary oval mass, measuring 6 cm in diameter, was found in his right lower lobe on roentgenologic examination The tumor was treated by pneumonectomy Postoperative microscopic examination confirmed the clinical diagnosis

23 *Meningioma* (Cushing), also known as arachnoid fibroblastoma (Mallory) has its highest incidence in the fourth and fifth decades of life This tumor arises from the arachnoid cells of the dura of the brain and the spinal cord The variations in its structural composition are well expressed in the classification of these tumors by Willis (1) Epithelioid form, (2) *Whorled* spindle celled form, (3) Psammoma form, (4) Fibrous form, (5) Ossified form, (6) Angiomatoid form (7) Sarcomatous form Pulmonary metastasis is infrequent Jurow reported a case with metastasis in the lung, with granular calcification

24 *Mixed tumors of the uterus* may develop when malignant

bronchus, the patient is likely to have attacks of coughing which are aggravated by swallowing liquid or solid nourishment In such instances cough may raise small food particles *Aspiration of the latter is bound* to cause choking spells Expectoration of hair occurs in teratoma which perforates into a bronchus

Wheezing denotes bronchial obstruction The latter may be either intrinsic, caused by tumor growth within the lumen of the bronchus or trachea *or extrinsic which is induced by compression of tumor masses in* the lung or affected enlarged lymph nodes in the mediastinum To these two factors one should add local edema of the bronchial mucosa which may be intense enough to account for a partial occlusion of the lower air passages

Pulmonary hemorrhage is not uncommon in metastatic lung tumors The degree of this symptom is variable The sputum may be blood tinged only or the patient may have repeated episodes of expectorations of large quantities of blood It is well to keep in mind that bouts of large and frequent pulmonary hemorrhages are encountered in metastatic *chorionepithelioma and in hemangioma*

Pain in the chest may be entirely absent, or it may be the presenting symptom It is described by the patient as a kind of heaviness, pressure, aching, gnawing, knife like or lancinating It is substernal or is localized laterally in the chest, with occasional radiation to the shoulder *or the back It is usually increased on coughing and deep breathing* and it may assume severe proportions at night Sudden, sharp pain is likely to be experienced by patients with metastatic chorionepithelioma

Hoarseness is brought about by paralysis of the recurrent laryngeal nerve, which is due to involvement of this structure by mediastinal tumor masses

Dyspnea is attributable to several causes

(1) The extent of tumor mass or masses in the lung

(2) Compression of the trachea or major bronchi or their partial occlusion by the new growth

(3) *Superimposed infection* of the lung with consequent added loss of respiratory surface

(4) Large pleural effusion with compression of several segments or lobes

(5) Inhibition of normal respiratory motions of the chest on account of pain due to extensive plastic pleurisy

(6) Diaphragmatic paralysis caused by involvement of the phrenic nerve along its course through the mediastinum

(7) *Spontaneous pneumothorax* brought about by the metastatic tumor

(8) Carcinomatous infiltration of the heart and pericardium

(9) Compression of large thoracic veins with consequent interference with the return of blood to the heart

(10) Severe anemia which results from the general toxic effect of the neoplasm

Cyanosis of various degrees is a manifestation of anoxia which is usually proportionate to loss of functional integrity of the cardiorespiratory system In some patients with massive neoplastic changes in the upper mediastinum there appears a livid pseudoflorid discoloration of the face Patients in this category may complain of marked swelling of the neck and may present a pitiful picture of respiratory distress

Constitutional symptoms are often absent Some patients have moderate or high fever followed by night sweats Fever is common in the presence of complicating pulmonary infection As the result of general intoxication associated with malignant tumors malaise anorexia considerable loss of weight even dehydration are noted in their advanced stages Noticeable pallor may be present It is brought about either by the toxic influence of the tumor or by blood loss through frank pulmonary hemorrhage within the neoplasm itself such as in chorionepithelioma or with expectoration of blood

Without being aware of the primary tumor patients may seek medical care on account of symptoms caused by pulmonary metastasis Even so and with due regard to this possibility special attention should be paid to corollary symptoms which originate from the primary tumor and its possible local complications Instances of this sort may govern one's diagnostic orientation Thus one should be reminded of chorionepithelioma by persistent uterine hemorrhages of dysgerminoma by psuedohermaphroditism of malignant tumors of the testicle by enlargement of and pain in the breasts of carcinoma of the kidney by low back pain with associated hematuria or carcinoma of the esophagus by dysphagia of Ewing's tumor by localized swelling and roentgenologically demonstrable newgrowth in the extremities Also it is well to consider the possibility of primary or metastatic neoplasms in case of obscure gastrointestinal complaints or abdominal pain

Cerebral manifestations may be induced by obstruction of the superior vena cava Symptoms which may occur in this connection include headache vertigo tinnitus loss of hearing somnolence loss of consciousness and epileptic seizures

bronchus, the patient is likely to have attacks of coughing which are aggravated by swallowing liquid or solid nourishment In such instances cough may raise small food particles Aspiration of the latter is bound to cause choking spells Expectoration of hair occurs in teratoma which perforates into a bronchus

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tended veins on the anterior chest wall which represent compensatory enlarged vessels of collateral circulation Through them, some of the blood from the tributaries of the occluded superior vena cava is carried to the inferior vena cava and thus to the right auricle

Limitation in the respiratory excursions of a hemithorax should direct one's attention to a unilateral lung lesion and its possible sequels such as massive atelectasis, large hydrothorax or localized emphysema

In some cases, the Oliver-Cardarelli sign, tracheal tug on swallowing is easily detectable

Clubbing of the fingers may be present Its pathogenesis is obscure These changes in the digits are far from being characteristic of metastatic lung tumors They are seen in large number of other diseases

Percussion and auscultation have considerable limitations in diagnosis Even so, they may prove useful adjuncts to assaying the patient's condition Large tumors are easily detectable by dull percussion note, decreased pectoral fremitus and absent breath sounds over the corresponding area The same holds true of complicating large pleural effusions Small tumors are easily missed on physical examination In a number of instances, however, they can be found on the basis of indirect evidence Not infrequently, small tumors may cause occlusion of one of the large bronchi and lead to massive atelectasis In other cases, they induce a partial occlusion of the bronchi and thereby result in obstructive emphysema of one lung These conditions, if otherwise unexplained, should focus one's attention on possible neoplastic growth Areas of atelectasis are predilectional sites for pathogenic micro-organisms Thus bronchopneumonia, infected bronchiectasis or lung abscess may develop as complications of a small tumor It is a good axiom not to be satisfied with the diagnosis of bronchiectasis or lung abscess until their origin has been definitely ascertained Also, it is well to keep in mind that unilateral bronchitis is always highly suspicious of bronchial obstruction When metastatic pulmonary tumor appears in the form of widespread, bilateral miliary nodules, the percussion note over the chest is hyperresonant on account of the extensive loss of lung tissues and the ensuing compensatory emphysema

General physical examination of the patient is of importance In chorionepithelioma in the male, both breasts are enlarged due to hypertrophy and contain freely movable, nontender masses The pectoral swelling can be easily mistaken for bilateral mastitis. On closer exami-

Diagnosis

It is almost banal to say that diagnostic awareness is the sine qua non of success in this respect Assuming that one is reasonably well versed in tapping hidden resources of his medical knowledge, it is still helpful to follow a reliable line of reasoning a line spun out of long and full clinical experience which will get one out of the labyrinth of conflicting diagnostic possibilities by the shortest and surest way

History taking is of assistance for more than one reason One may learn about the incidence of malignant tumors in the patient s antecedents and relatives There appears to be some unknown form of hereditary conditioning which probably acts as a basic contributory factor in the development of malignant new growth The role of occupational hazards in relation to the genesis of these tumors has been discussed in connection with primary malignant lung tumors In women history of abnormal gestation or irregular vaginal bleeding may point toward the origin of a pulmonary metastasis Chorionepithelioma should be thought of when there is vaginal discharge of grape like, transparent vesicular structures The latter vary in size from microscopic to 1 to 2 cm in diameter These friable spherical units are filled with watery fluid Also, subjective and objective symptoms and signs of endocrine imbalance may guide one toward finding the source and character of metastatic tumors in both men and women

Physical examination may reveal important clues to the correct diagnosis It is mandatory to inspect the patient carefully, with particular reference to the chest Neoplasms localized in the apical region are often responsible for the Hare Horner-Claude Bernard syndrome (enophthalmos, ptosis, miosis) It develops as the result of involvement and paralysis of the cervical sympathetic nerve *It is mandatory* to search for the so called sentinel nodes (Troisier Virchow) in the supraclavicular fossae Although such enlarged, painless lymph nodes are common in association with carcinoma of the stomach they may be encountered in malignant tumors of the lung When the latter are accompanied by massive neoplastic changes in the upper mediastinum—whether these changes are metastatic or primary—signs of obstruction of the superior vena cava may become evident These are puffiness cyanosis and lividity of the face and neck, bulging staring eyes, suffusion of the conjunctiva, edema of the face, neck arms, thoracic and upper abdominal wall, congestion edema and cyanosis of the mucous membrane of the mouth, pharynx and larynx There are prominent, dis-

tended veins on the anterior chest wall which represent compensatory enlarged vessels of collateral circulation Through them, some of the blood from the tributaries of the occluded superior vena cava is carried to the inferior vena cava and thus to the right auricle

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nation, however, one finds that clear fluid (colostrum) can be expressed from the nipples In some of these cases colostrum formation may be slight or absent, for considerable time is necessary for the functional hypertrophy of the underdeveloped male breast under the effect of hormones liberated by the tumor

Examination may reveal the presence of a tumor mass in the scrotum enlarged inguinal lymph nodes, pelvic or abdominal masses, enlargement of the uterus, stone like induration of the prostate, ascites or swelling along the shaft of long bones Gastrointestinal x ray studies with barium or double contrast medium may show the primary site of the neoplasm Special attention should be paid to the passage of barium through the esophagus so as to detect stenosis due to carcinoma of this structure or to extrinsic pressure by a mediastinal mass Swallowing small capsules filled with carmin may be followed by expectoration of red stained sputum indicating communication between the carcinomatous esophagus and the respiratory tract Urograms are of value in locating neoplastic growth in the kidneys and bladder

One should take full advantage of pertinent information obtainable with x rays It is advisable to resort to roentgenography and fluoroscopy in all cases In addition to standard postero anterior chest films x ray pictures of the chest should be taken in the lateral and both oblique positions so as to visualize and accurately to localize the tumor If case findings are not immediately obvious, the retrocardiac region and the costophrenic sulcus should be thoroughly scrutinized A better view can be obtained of the latter with the patient in a slightly lordotic position Small tumors causing partial (check valve type) occlusion of a bronchus may be recognized from the presence of obstructive emphysema when films taken in maximum inspiration and expiration are compared Chest films taken in the standard position are informative of shape size density relative distribution and to a certain extent location of the neoplasm The latter appears on the roentgenogram either as a single opacity or as multiple shadows Multiple shadows are of five kinds

(1) Miliary nodules widely distributed throughout both lungs,

(2) Snow flake like, small opacities of the same distribution,

(3) Ill defined shadows up to 3 cm in diameter scattered in both lung fields,

(4) Sharply demarcated, dense round shadows, varying in size from that of a quarter to a 50 cent piece (from 23 to 30 mm),

(5) Massive, well defined somewhat oval shadows which are much larger than the ones mentioned

Shadow cast by a solitary tumor may be localized in any part of the lung apical basal or in the midlung It may be peripheral or central Tumors centrally located present a shadow which is fused with that cast by the hilar structures particularly when there is neoplastic involvement of the lymph nodes in this area Solitary tumors lying in the lung field are usually well delineated In some instances their border is hazy on account of perifocal hemorrhage Perihilar neoplasms which may be asymptomatic for years cast a shadow of irregular, infiltrative outline To determine the exact location of some of the larger basal tumors and also to differentiate them from eventration of the diaphragm diaphragmatic hernia and subdiaphragmatic disease it may be necessary to give the patient barium for visualization of the gastrointestinal tract Diagnostic pneumoperitoneum may be called for This is a useful simple and safe procedure which can be easily carried out by any physician of average manual dexterity Large tumor masses occasionally show rarefaction in their center indicative of cavity formation This possibility calls for its differentiation from cavities seen in various lung infections particularly in lung abscess tuberculosis and fungus disease and possibly in syphilis silicosis congenital cystic disease of the lung cystic emphysema in pneumonia echinococcus cyst simple mediastinal cyst and mediastinal gastric cyst

Standard roentgenograms of the chest should be studied for the presence of erosion of the bony structures and also for atelectasis pleural effusion and emphysema The extent of atelectasis depends upon the size of bronchial tube occluded Atelectasis may be plate like segmental lobar or massive (multilobar) Findings characteristic of this condition are given in details in the respective chapter Small pleural effusions cast a roughly triangular shadow with its base on the diaphragm Large pleural effusions may entirely obscure the underlying neoplasm besides causing an enlargement of the corresponding hemithorax with widening of the intercostal spaces It is mandatory to remove the effusion by aspiration for determining its specific gravity cell content with special emphasis on search for malignant cells and other properties which are of diagnostic interest Removal of the fluid from the chest permits better visualization of the lung fields In some instances valuable information can be gained by replacing some of the aspirated fluid with air and then do a thoracoscopic examination The latter procedure can

Prognosis

There are great variations in the behavior of metastatic new growths of the lung Even so malignant tumors of this organ should be looked upon with grave anticipations *Such attitude is particularly justifiable* when there are multiple foci of metastasis Exceptions *to the usual* slow or rapid but inevitable deterioration of the patient are unfortunately, very rare and they are mentioned only for the sake of curiosity An instance in point was the patient of Speed who remained well for 13 years in spite of multiple pulmonary metastases which originated from a distant focus of osteosarcoma Lampe and Zatzkin called attention to pulmonary metastases of pseudoadenomatous basal cell carcinomas (mucous and salivary gland tumors) on account of their protracted course which may extend over a period of years During the sluggish growth of these metastatic foci, the patient may remain asymptomatic and comfortable for years Pendergrass and his associates reported 33 per cent five year survival for patients with malignant tumors of the testicle associated with metastasis in the mediastinopulmonary structures These patients were treated with orchidectomy and with pre and post operative x ray irradiation At the same time, they emphasize that following x ray therapy and apparent complete retrogression of neoplastic *changes recrudescence* and rapid spread of the tumor may take place More favorable are the prospects in women with *chorionepithelioma* Extensive metastatic lung involvement may completely clear after hysterectomy for the primary neoplasm even when no x ray irradiation is applied to the lungs

Treatment

Evidence is accumulating in support of surgical removal of solitary metastatic lung tumors Depending upon given circumstances, lobectomy or pneumonectomy are the types of intervention advised *Old* age in itself is no contraindication to major thoracic surgery provided cardio respiratory incompetence renal failure, metastasis to other organs and inoperability of the primary tumor do not interdict it Surgical intervention may be required from a few months to 13 years after *the removal of the primary neoplasm* Reports of the length of survival following these operations are favorable and justify wider application of this method of treatment Nowadays hundreds of lobectomies are reported by various surgical groups *without a single operative death*

Snapper, in 1947, began to use stilbamidine, together with low animal protein diet for the treatment of multiple myeloma He noted re-

lief from subjective symptoms and temporary cessation in the progression of the disease The drug is given intravenously in doses of 150 mg daily to a total of 3,000 to 6,000 mg In view of disturbing toxic reactions and the only temporary benefit, Gellhorn and Jones recommend that stilbamidine should be used only as a last resort in the treatment of multiple myeloma Loge and Rundles, in 1949, observed striking improvement following the administration of urethane (ethyl carbamate) In a period of eight to 10 weeks they administered orally from 120 to 290 Gm of the drug

Reference has been made to the disappearance of metastatic chorion epithelioma following supracervical or panhysterectomy for the primary neoplasm Also these metastatic tumors respond favorably to x ray irradiation Marked regression of metastatic lung tumors originating from malignant new growths in the testicle has been reported by a number of clinicians For postoperative x ray therapy in these cases, Pendergrass and his associates (1946) recommended the following schedule

> 'The primary drainage areas, situated about the celiac axis, should be completely treated first, followed by successive fields upwards to include finally the left supraclavicular area and downwards to include the inguinal regions and pelvis The recommended treatment factors are 200 KV, 15 ma, 0 5 mm Cu plus 1 mm Al, 80 cm target-skin distance The half value layer with these factors is 0 9 mm Cu The treatment fields should extend at least 10 cm to each side of the midline Each field, anteriorly and posteriorly, should receive at least 1,600 r measured in air, in divided daily doses'

X ray irradiation is permissible as a palliative measure when the primary tumor is inoperable or the patient declines surgical intervention Of course, a prerequisite of such treatment is the radiosensitiveness of the neoplasm

In view of the observation that in some instances, carcinoma of the breast has more malignant tendencies during pregnancy, it was advocated that oophorectomy should be performed to exert a suppressive influence upon the breast cancer and its metastatic foci Also, the administration of testosterone propionate and x ray irradiation of the ovaries has been practiced for the same purpose Klass used testosterone propionate in doses of 50 mg three times weekly for four weeks before mastectomy, and in doses of 75 mg twice weekly postoperatively He

observed notable regression of the patchy, widely distributed foci of metastatic carcinoma in the lung It is well to inform the patient prior to the beginning of this treatment *that the drug has definite masculinizing effect* In a case of pulmonary metastasis from adenocarcinoma of the corpus uteri Freed and his associates observed complete disappearance of the chest metastasis following a course of testostorone propionate injections

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CHAPTER IX

LUNG DISEASES OF VASCULAR ORIGIN

PULMONARY EMBOLISM AND INFARCTION

By WILLIAM V LEARY, M D AND HERMAN J MOERSCH, M D

THE PORTION of medical history that deals with pulmonary embolism and infarction is a chapter which will please the most exacting reader It is adorned with names of famous men, the knowledge of the subject evolves in an orderly manner with little empiricism, and though the last word has by no means been written, a satisfactory climax is provided

The first anatomic description of pulmonary infarction was presented by Laennec in 1823, who correlated the clinical picture with the pathologic findings The importance of his contribution is not minimized by the fact that he appears to have regarded the lesion as analagous to cerebral hemorrhage, referring to it as "pulmonary apoplexy" During the subsequent years numerous investigators noted the association of these infarcts and clots in the pulmonary arteries, but interpreted them as being due to phlebitis The doctrine of embolism was established by Virchow, following a brilliant series of anatomic, experimental, and clinical investigations over a 10-year period, 1846 to 1856 This work of Virchow has been called a "model of scientific research' by William Welch It was Welch and Mall who later in 1887 investigated the problem of hemorrhagic infarction and introduced the modern concept of the role of circulatory stagnation in the production of these lesions The era of specific therapy may be considered to date back to 1916 with the discovery of heparin by McLean, although this substance did not become available for clinical use until 1933 when Charles and Scott produced a sufficiently pure product. In the 1930's Homans introduced venous ligation as a measure for the prevention of pulmonary embolism With the discovery of dicumarol by Link and his associates in 1941, the present status was reached a position which must be regarded as satisfactory even if no more than the changed at

titude of physicians toward pulmonary embolism in the past 10 years is regarded

Incidence

The incidence of pulmonary embolism can only be approximated A comprehensive statistical analysis of all published reports is impossible since there is no uniformity in the manner in which the various authors have presented their statistics Furthermore the results of such a composite study would encounter the objection that the incidence varies with the interest of the clinician and pathologist in the subject Belt has stated that probably no other postmortem finding is more readily overlooked Hampton and Castleman added weight to this statement when they found an apparent increase of 50 per cent in the number of cases of pulmonary embolism and infarction in the same institution through the use of postmortem roentgenograms of the chest The variability of statistics is best illustrated by comparing an incidence of 28 per cent pulmonary emboli in one necropsy series with the statement by a physician that there had been no cases of pulmonary embolism over a two year period in a large general hospital

The incidence of postoperative pulmonary embolism in several large series of cases varied from 0 10 to 0 67 per cent of all cases in which operations were performed In several series of necropsy cases 2 to 6 per cent of all postoperative deaths were due to pulmonary embolism McCartney found that of 1,499 deaths following trauma, 4 per cent were attributable to pulmonary embolism Contrary to general belief, pulmonary embolism occurs more frequently in medical than in surgical patients Over a 10 year period at the Massachusetts General Hospital pulmonary embolism or infarction was demonstrated in 0 60 per cent of the medical cases whereas the incidence in the postoperative cases was 0 24 per cent

Several large series of unselected necropsy cases have revealed an incidence of fatal pulmonary embolism which varies from *2 07 to 6 7* per cent Transferring the smaller of these percentages to the general population, Barnes has emphasized the importance of the problem, he has estimated that the annual death rate in the United States from pulmonary embolism is 34,000, and that of all the persons alive in the United States in 1937, 3,000,000 would eventually die of pulmonary embolism The higher figure quoted by Moran (*6 7 per cent*) may give a more accurate picture of the general incidence since he was dealing with patients of an older age group, very few of whom had been

operated on When it is realized that many of these deaths are now preventable, the importance of the problem needs no further comment

Pathogenesis of Thrombo-Embolism

Aschoff has presented a clear conception of the morphologic development of venous thrombosis From his studies he was led to the conclusion that the initial process is one of agglutination, after which the major portion of the thrombus is formed by simple coagulation The earliest changes consist of an accumulation of platelets arranged in a definite framework and tightly adherent to the wall of the vessel Other cellular elements become enmeshed in this enlarging framework until the vessel is completely occluded Most writers have stated that this initial process usually occurs in the smaller veins of the calf muscles or the plantar veins The evidence supporting this conclusion has not been convincing, however, and there are probably many cases in which the process began in the large veins of the lower extremities From this point of occlusion a red coagulation thrombus extends in a proximal direction Early in its development the growing end is not adherent to the vessel wall and may extend for a variable distance into the large veins of the lower extremities

The importance of differentiating phlebothrombosis from thrombophlebitis has received undue emphasis in medical writing, since any clot within a vein is a potential embolus including the thrombophlebitis of thromboangutis obliterans, and since thrombophlebitis is in most instances a later stage of phlebothrombosis

Barker has presented his concept of venous thrombosis as a disease occurring in episodes The first episode is usually in the smaller veins of the leg A portion of the entire thrombus may detach soon after its formation If it is not detached, or only a portion is detached, organization begins, producing an inflammatory reaction in the wall of the vein with the signs and symptoms of thrombophlebitis The danger of embolism is now passed, unless a second episode of venous thrombosis occurs with propagation of the thrombosis into a larger, more proximal vein This series of events may be repeated several times, and the successive thrombi will undergo organization or produce emboli If this process invades a sufficiently large vein and detachment occurs, fatal pulmonary embolism may result. This concept of thrombo-embolism is based on analysis of a large clinical experience and clearly indicates

that any feeling of safety in the presence of thrombophlebitis is unwarranted

Barker stated that a patient who has had a postoperative pulmonary embolus and survived has a 30 per cent chance of having another embolus and an 18 per cent chance that such an embolus will be fatal

The important role that thrombophlebitis plays in pulmonary embolism is well exemplified in a review of 897 cases of thrombophlebitis studied by Barker and his associates who found that pulmonary embolism or infarction which could be demonstrated either clinically or in postmortem findings developed in 140 patients (15 6 per cent) In 51 of the 897 patients (5 7 per cent) the embolus proved fatal In a review of 343 cases of fatal pulmonary embolism Barker and his associates found that 40 per cent of the patients presented no clinical or postmortem evidence of venous thrombosis or thrombophlebitis whereas 45 per cent presented no clinical evidence of venous thrombosis or thrombophlebitis but such lesions were found at the time of necropsy

Etiology of Venous Thrombosis

In spite of a great amount of investigation and speculation the specific combination of factors leading to thrombosis remains elusive The greatest obstacle has been the difficulty in separating the various causative factors since they are usually present in combination and one may influence the other Ochsner stated the opinion that the fundamental abnormality is one of increased coagulability of the blood with circulatory stasis as the precipitating factor

Alteration of the Flow of Blood Slowing of the circulation is probably an important factor in the production of thrombosis in many cases In laboratory studies Aschoff noted that complete cessation of the flow of blood did not cause thrombosis and Welch has stated that simple slowing is an inefficient method of producing intravenous clotting From the investigations of Aschoff, it would appear that the formation of eddy currents is equally as important as slowing of the flow in the formation of the initial agglutination thrombus There are numerous conditions which may contribute to circulatory retardation or formation of eddies (1) diminution of the vis a tergo through impaired cardiac function or vasoconstriction (2) increased venous pressure with widening of the lumen of the vein producing ampulla like widenings above the venous valve (3) decrease in the negative intra

thoracic pressure as a result of hypopnea, (4) diminished contraction of the muscles of the extremities, and (5) *local pressure on veins, such* as occurs at Poupart's ligament or at points where veins are crossed by arterial trunks The importance of venous stagnation in the production of venous thrombosis is evidenced by the reports of "shelter deaths" in England during the blitz of 1940 Simpson found fatal pulmonary embolism in 24 presumably healthy persons, as compared to four cases in the preceding year He attributed this increase to the practice of *sitting for long periods of time in* deck chairs or similar seats with the legs dependent

ALTERATIONS IN THE CELLULAR ELEMENTS OF THE BLOOD Although it is well known that the platelets undergo a physiologic increase after any trauma (surgical, accidental obstetrical), the factors leading to agglutination in a platelet thrombus are not understood It has been postulated that the increased agglutinability is the result of changes in the surface electrical charge, which in its turn is the result of alterations in the albumin globulin ratio Further in vivo investigations such as those of Knisely and associates into the phenomenon of "sludging may shed a good deal of light on the formation of venous thrombi

ALTERATIONS IN THE BLOOD PLASMA Since simple stagnation does not lead to thrombosis, there must be a factor of increased coagulability to explain the production of the red thrombus As in the case of the cellular elements of the blood following trauma the increased coagulability of the plasma is a physiologic protective mechanism

Knowledge regarding the factors leading to this increased coagulability is scant It is generally thought to be associated in some manner with the absorption into the blood of various substances released by traumatized cells The chief virtue that can be attached to such an explanation is its lack of specificity The evidence is inconclusive that coagulability of the blood is increased by the administration of digitalis, aminophylline or penicillin Among the specific changes in the components of the blood which have been incriminated are increases in viscosity, in the amounts of prothrombin, globulin, fibrinogen peptidase and calcium and in anti tryptic power and decreases in carbon dioxide proteins heparin or heparin tolerance and the presence of fibrinogen B profibrin) In addition to the various components of the blood, the autonomic nervous system plays a role in coagulation of the blood Adrenergic impulses increase coagulability, whereas cholinergic impulses

have an inhibitory effect The manner in which this is accomplished is unknown

ALTERATIONS IN THE VESSEL WALL Endothelial damage is the least important of the factors in venous thrombosis Except in cases of primary thrombophlebitis, it does not produce thrombosis, although it may act indirectly in the influence of other factors It is felt that the condition of the endothelium may be of importance in producing adhesion of the framework of platelets to the vessel wall

Predisposing Factors in Thrombo-Embolism

SURGICAL PROCEDURES Several factors in the postoperative state favor intravenous clotting Prolonged immobility of the lower extremities, hypopnea and generalized vasoconstriction promote stagnation of the venous blood Shock and dehydration contribute to such a state of affairs It has been noted previously that operations usually are followed by an increase in the platelets and the coagulability of the blood

Various authors have attempted to determine by statistical studies the relation between the incidence of thrombo-embolism and the type of operation Because of the variation in different series and the various attending circumstances other than the operative procedure itself it is impossible to arrive at any definite conclusions In some institutions amputation through the thigh carries a high risk of pulmonary embolism Veal has reported an incidence of 14 9 per cent of fatal pulmonary complications following major amputations. Since he was able to reduce this to 1 2 per cent by ligation of the femoral vein, the conclusion is implied that the pulmonary complications were largely embolic Of 49 patients who underwent amputations in Allen s series six died of pulmonary embolism

The analyses of Barker and his associates indicate that the amount of tissue resected or destroyed by the operation is an important factor After 10,938 laparotomies in which extensive resection of tissue (gastric resection, splenectomy resection of small intestine and hysterectomy) was performed at the Mayo Clinic, the incidence of pulmonary embolism was 1 76 per cent and the incidence of fatal pulmonary embolism was 0 68 per cent At the same institution the respective incidence after all operations was 0 50 and 0 20 per cent respectively

The type of anesthesia appears to have no effect on the incidence of thrombo embolism

OBSTETRICAL DELIVERY The incidence of thrombo-embolism fol

lowing parturition rather closely parallels that after operation, although in most series the incidence of fatal embolism is smaller The factors which operate in the production of thrombosis would appear to be similar to those that produce it after operation

TRAUMA McCartney found an incidence of fatal pulmonary embolism of 4 per cent in a group of 1,499 necropsies in cases in which death was due to mechanical injury During the same years the incidence of pulmonary embolism was 2 6 per cent in cases in which death was not due to trauma Of the group of patients who had posttraumatic pulmonary embolism 80 per cent had sustained injuries of the lower extremities, usually a simple fracture of the femur Eleven (10 per cent) of 110 consecutive patients who had fracture of the hip in Allen s series died of massive pulmonary embolism McCartney stated that these findings can be explained by the fact that fracture of the femur commonly occurs in patients of advanced age and by the prolonged rest and strict immobilization required after such injuries Additional predisposing factors were the high incidence of heart disease in this group and the trauma to blood vessels that complicates such fractures It is of interest to note that posttraumatic pulmonary embolism tends to occur later than the postoperative variety In half of his cases the pulmonary embolism occurred more than two weeks after the injury, and in a fourth of them the interval was more than four weeks

CARDIOVASCULAR DISEASE White has shown that pulmonary embolism and infarction are frequent complications of heart disease and may occasionally simulate congestive failure Though they may complicate any type of cardiac disease the highest incidence is found in (1) coronary artery disease, particularly following acute myocardial infarction, (2) rheumatic heart disease, particularly mitral stenosis with auricular fibrillation, and (3) hypertensive heart disease

Of 60 patients who died within six weeks after acute myocardial infarction, Woods and Barnes found that six had died of massive pulmonary embolism Analysis of other series of necropsies indicates that the incidence of thrombo-embolism is high in such patients and is the main or contributory cause of death in 10 to 15 per cent Carlotti and his associates found that 70 8 per cent of a large group of non surgical patients who had pulmonary embolism had various types of heart disease, and a third were in congestive failure. Levine and White studied 52 patients with severe mitral stenosis, 23 of whom

had congestive failure, in these 23 cases the incidence of pulmonary infarction was 61 per cent

In the cases of hypertensive heart disease with failure in the same series of necropsies the incidence of pulmonary infarction was 21 per cent The influence of heart disease on the eventual outcome of postoperative pulmonary embolism has been investigated by Morton and associates In cases in which postoperative pulmonary emboli were found at necropsy, the emboli were considered as the immediate cause of death in 59 per cent of the group without cardiac disease, 92 per cent of the group with cardiac disease and in all of the patients with cardiac decompensation

The source of the embolus in heart disease is usually the lower extremities, although the chambers of the right side of the heart may occasionally loose a thrombus into the pulmonary artery In congestive cardiac failure the increased venous pressure with the slowing of the circulation is the obvious cause of thrombosis Increased viscosity of the blood and hyperprothrombinemia have been observed by some investigators With myocardial infarction without congestive failure numerous factors become operative Such patients are often prostrated and practically immobile for many days, frequently at the advice of the physician The contraction of the left ventricle may be greatly enfeebled with resultant drop of arterial pressure and diminished vis a tergo Lastly, coronary disease is in general a disease of older age

Pulmonary embolism may simulate heart disease in two ways (1) through the production of acute cor pulmonale, and (2) through the production of pulmonary edema

Advancing Age Although pulmonary embolism has been reported to occur in infancy, statistical evidence is convincing that it is a complication of advancing age The incidence is small during the first four decades—approximately 85 per cent of the patients who have it are more than 40 years of age Numerous fact[illegible] been advanced to explain these figures The [illegible]usible are [illegible]sing incidence of cardiovascular disease a[illegible] d dec[illegible] scular activity which attend the advance [illegible] changes are probably of secondary [illegible]

Infectious D[illegible] pu[illegible]
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may result from any febrile illness No specific cause has been advanced for this, but it would be expected that prolonged immobility is the precipitating mechanism On this basis a higher incidence of thrombo-embolism would be expected in those diseases which confine the patient to bed in a moribund state for a period of time greater than several days Dehydration increased viscosity of the blood and derangement of the clotting mechanism are other possible factors

Prolonged Immobility The abuse of rest in bed has received much well-deserved condemnation in the last few years As has been mentioned prolonged immobilization probably is responsible in a large measure for the relatively high incidence of pulmonary embolism after operations and trauma and in the infectious diseases It probably plays an equally large role in cases of debility and cachexia In this connection it is interesting to note the low incidence of pulmonary embolism in patients who have pulmonary tuberculosis The obvious reason for this is that such patients are usually not seriously ill and move about in bed frequently From the standpoint of pulmonary embolism, at least, immobilization of the lower extremities is of greater danger than mere rest in bed

Malignant Disease Many years ago Trousseau called attention to cancer as a cause of peripheral thrombosis and embolism Barker found carcinoma in 27 of 58 cases of thrombophlebitis complicating noninfectious diseases The most comprehensive study of this subject was made by Sproul who revealed a 56 2 per cent incidence of thrombosis in 16 cases of carcinoma of the body or tail of the pancreas In five cases the thrombi were multiple and in four of these there were pulmonary emboli In the same study Sproul found venous thrombosis in 32 of 147 cases of carcinoma of the colon and in 12 of 81 cases of bronchiogenic carcinoma The precipitating factors are unknown, the theory which has been invoked is that necrosis of carcinoma cells releases various unknown substances which increase the coagulability of the blood

Diseases of the Blood After abdominal hysterectomy, Barker and his group found postoperative thrombo-embolism in 9 3 per cent of the patients who had various blood diseases and in only 1 9 per cent of the patients who had no predisposing conditions Severe anemia and polycythemia vera are the worst offenders and thrombosis is not an uncommon complication of leukemia It is recognized that various factors in the clotting mechanism are abnormal in diseases of the blood,

but the exact manner in which they precipitate thrombosis is not understood

DISEASES OF THE VEINS The presence of varicosities or old thrombophlebitis increased the incidence of postoperative thrombo-embolism from 1 9 to 5 6 per cent in Barker's series It is doubtful that varices themselves give rise to important emboli, but are rather of importance in the production of deep thrombosis through stagnation of the deep circulation Thrombosis of a superficial varicose vein could reach serious proportions by propagation into a deep vein

Idiopathic recurrent thrombophlebitis is complicated by pulmonary embolism in approximately 10 per cent of the cases Although rare, the occasional occurrence of pulmonary embolism in thromboangiitis obliterans is evidence that any clot in a vein is a potential embolus even though it may arise from a primary disease of the vein

MISCELLANEOUS FACTORS Among these factors are smoking, constitutional diathesis and seasonal variation Pale skinned, asthenic and weak muscled individuals are considered more likely to have thrombo-embolism than others and numerous investigators have presented statistical evidence that the incidence of postoperative pulmonary embolism is higher in obese patients than in a control group of normal weight Authors are not in agreement on the subject of seasonal variation as a causative factor Some have found no such variation, whereas others have stated that the incidence is higher in the winter months and in the northern states The latter have implicated the grippal infections as the causative factor

The Pathologic Physiology of Pulmonary Embolism

In 1924 German investigators outlined three possible causes of death following pulmonary embolism (1) acute asphyxia, (2) gradual failure of the right side of the heart, and (3) immediate death in shock They considered that the last named cause was due to reflex stimulation of the vagus which produced cardiac standstill or coronary constriction Since that time a large amount of investigation has been focused on the question of reflex stimuli arising from pulmonary embolism

Both anatomic and physiologic evidence indicate the presence of a pressor receptor in the wall of the pulmonary artery which is similar in its action to the carotid sinus This is sometimes referred to as the "*glomus pulmonum*" and is capable of initiating depressor reflexes in the systemic and coronary circulations in the presence of pulmonary hypertension

The fall in blood pressure in systemic circulation may be due to insufficient flow of blood to the left side of the heart because of the mechanical obstruction to the pulmonary circulation

Death through acute asphyxia corresponds to the "asphyxique" (Rochet) type of pulmonary embolism, whereas the immediate death in shock corresponds to the "syncopale" clinical picture described by Rochet Experiments on animals indicate that the latter picture is produced by massive pulmonary embolism with occlusion of the main pulmonary arteries (probably requiring 80 per cent obstruction or more) The asphyxial type on the other hand is produced by occlusion of the peripheral vascular bed Although complete protection against pulmonary embolism was not afforded, the work of Jesser and de Takats as well as others seems to indicate that vagotomy or administration of atropine ameliorates the symptoms in both the massive and peripheral types of pulmonary emboli De Takats and Jesser have carried out experiments in which they have visualized the pulmonary circulation and the tracheobronchial tree of dogs After the production of artificial emboli in the pulmonary artery, they were able to demonstrate dilatation of the right side of the heart and vena cava The changes in the bronchograms were even more striking, the main bronchi became invisible, and the opaque material was squeezed into the terminal radicles with subsequent bullous dilatation of the finer bronchi and patches of emphysema

They found atropine to be effective in the prevention of bronchospasm, whereas papaverine was only partially effective Papaverine, however, produced relaxation of the pulmonary vessels Although epinephrine could be expected to produce a bronchial relaxation, it increased resistance in the pulmonary vascular bed and pulmonary edema was the invariable result

The role of the coronary circulation in pulmonary embolism is still being argued De Takats has presented evidence that constrictor impulses are mediated through the vagus, whereas Malinow and co-workers have denied that any such reflex exists Horn, Dack and Friedberg found anatomic evidence of myocardial ischemia in eight of 42 cases of fatal pulmonary embolism and could find no other cause for the changes except the embolism They pointed out that myocardial ischemia may be produced by any one or a combination of three factors (1) peripheral shock with lowering of the mean pressure in the

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The status of the pulmonary venous circulation appears to be the most important single factor in determining whether or not pulmonary infarction will result from embolism In the laboratory animal arterial obstruction readily produces hemorrhagic infarction if the venous circulation is first impeded The clinical counterpart of this is found in the frequency of hemorrhagic infarction in congestive heart failure, particularly that due to mitral stenosis There is indeed a widespread belief that pulmonary infarction cannot occur unless some degree of passive congestion exists It is impossible to reconcile this belief with the occasional occurrence of pulmonary infarction after pulmonary embolism in young and otherwise healthy individuals in whom no evidence of heart disease can be demonstrated In such cases, factors as yet unknown must be called to account There is evidence that bronchial stenosis or infectious processes may be important factors in the out come

Pathology

GROSS PATHOLOGY In his description of pulmonary infarction, Laennec noted that the lesions are often multiple and that the lower lobes of the lungs are the most frequently affected Various series of postmortem material indicate that the infarctions are multiple in approximately 60 per cent of cases The figures of Hampton and Castleman are representative of the literature in general with respect to the distribution of infarcts They found that 74 per cent were located in the lower lobes, 43 per cent in the right and 31 per cent in the left Involvement of the upper or middle lobes usually occurs in combina tion with a lesion of one or both lower lobes

The lesions are always subpleural in location with involvement of one or more pleural surfaces The textbook description of a triangular-shaped lesion has been denied by Hampton and Castleman who demonstrated an irregular or rounded configuration This difference of opinion probably is due to the fact that they examined the lungs in the inflated state Infarcts vary in size from 0 3 cm in diameter to involvement of an entire lobe The cut surface of an infarct is firm, red to black-red, and sharply circumscribed There may be slight com pensatory emphysema in the surrounding pulmonary tissue which is otherwise normal

MICROSCOPIC PATHOLOGY During the first two days after em

coronary arteries, (2) anoxemia due to mechanical interference with pulmonary flow, and (3) constrictor reflexes

Pathogenesis of Pulmonary Infarction

The doctrine of Virchow that pulmonary infarction is the result of mechanical arterial obstruction by embolism or thrombosis in situ has gained general acceptance Sporadic objections have been raised on the grounds that pulmonary embolism does not invariably produce infarction and infarction has occurred in cases in which no obstruction could be demonstrated The latter objection is scarcely valid since small emboli are easily overlooked in the usual method of examining the lungs at necropsy The answer to the other problem is not so simple Simple obstruction of a branch of the pulmonary artery will not produce infarction in the experimental animal In the attempt to answer the question of why embolism produces infarction in some instances and not in others, the collateral circulation of the lung has received great emphasis

The collateral vessels in the pulmonary arterial circulation are probably of little importance in the maintenance of the blood supply to the obstructed portion Injection of radiopaque material into the pulmonary artery has indicated that collateral anastomoses are at the capillary level In the presence of an embolus, injection of radiopaque material under high pressures failed more than partially to fill the vessels distal to the obstruction Since the pulmonary arterial pressure is high only after relatively massive embolism, it seems improbable that these collateral anastomoses are a source of blood supply

On the basis of certain anatomic consideration, the bronchial circulation appears to be the source of the major collateral supply of blood in the lungs Virchow called attention to hypertrophy of the bronchial artery after pulmonary embolism, and this has been confirmed by injection experiments This hypertrophy has been limited to the portion *of the artery extending to the affected segments* Studies of blood flow in the bronchial arteries suggest that they are incapable of substituting for the pulmonary flow, but Bruner stated that these findings cannot be interpreted too literally in the presence of pulmonary embolism when the pulmonary arterial pressure is reduced to a minimum distal to the obstructed segment After reviewing all the evidence, Bruner stated that the bronchial artery provides the only positive inflow into a pulmonary infarct Since the metabolic demands of pulmonary tissue are

low, this flow is probably sufficient to prevent necrosis if other factors are not operative

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bolism there is marked congestion of the capillaries, and the alveolar spaces are filled with blood After the second day, necrosis of the alveolar walls begins, along with regeneration of the erythrocytes During the second week organization of the infarct begins and granulation tissue appears at the periphery and migrates inward This requires a variable length of time for completion depending on the size of the infarct The center of large infarcts may remain hemorrhagic indefinitely During the process of organization the infarct shrinks in size As the granulation tissue is ultimately replaced by scar tissue, the final result of an infarct will be a small fibrous scar which may be difficult to find at necropsy

If the collateral circulation to an infarct is adequate, necrosis of the alveolar wall does not take place and the lesion heals by resolution and leaves no residual scar To such lesions Wharton and Pierson have given the name "incomplete infarction" In the opinion of Hampton and Castleman incomplete infarction occurs with much greater frequency than is generally recognized The failure of the pathologist to find such lesions with greater frequency is explained by two circumstances (1) complete resolution requires only a few days, and the infarct may have disappeared before death occurs, and (2) adequate collateral circulation presupposes a healthy pulmonary circulation and ultimate recovery of the patient, barring massive pulmonary embolism The microscopic appearance of incomplete infarcts is similar to the early stages of a true infarct

An occasional complication of pulmonary infarction due to bland embolism is the development of a pulmonary abscess In 23 of 550 cases (4 2 per cent) of pulmonary infarction studied at necropsy, Levin, Kernohan and Moersch found abscess formation In six of these cases there was secondary empyema Of even rarer occurrence is the occasional infarct which undergoes central liquefaction with cavitation

Diagnosis of Pulmonary Embolism and Infarction

The diagnosis of pulmonary embolism is relatively easy when it is manifest in its classic manner Small emboli, however, frequently produce an atypical clinical picture and in some instances occur without any symptoms For this reason the diagnosis of pulmonary embolism is often extremely difficult or impossible White has stated that pulmonary embolism is frequently overlooked even by experienced physicians and the clinical diagnosis is made in probably less than half of the medical cases

in which it is discovered at necropsy The importance of detecting small emboli becomes obvious when it is realized that more than a third of all fatal pulmonary emboli are preceded by smaller, nonfatal emboli Prevention of these fatal episodes depends on the proper diagnosis of the earlier lesions with the prompt institution of anticoagulant therapy or venous ligation No rigid rule can be applied to each individual patient, but in general, it can be stated that if there is reasonable suspicion that pulmonary embolism has occurred, treatment should be instituted promptly A policy of further observation in such cases is indefensible The treatment is practically harmless, the next pulmonary embolus may be fatal

Before proceeding with the direct diagnostic attack on the pulmonary complication the physician should first review certain pertinent data to ascertain if the patient is a likely candidate for pulmonary embolism These data may be looked on as collateral evidence and include the patient's age, weight the primary disease, the cardiac status of the patient a history of thrombophlebitis or pulmonary embolism, and the presence of any blood dyscrasia or infection If the patient has been operated on, the type of operation must be taken into consideration as well as the time which has elapsed between the operation and the pulmonary complication In most cases pulmonary embolism occurs during the second week after operation, although in about a fourth it happens in the first week and it has been reported on the day of operation Physical examination should include inspection and palpation of the lower extremities for varicose veins and any evidence of venous thrombosis though such evidence is lacking in the great majority of cases of pulmonary embolism.

Symptoms and Signs The manner in which pulmonary embolism manifests itself depends largely on the size of the embolus Large emboli produce symptoms through obstruction of the pulmonary artery If this is complete or nearly complete, death occurs almost immediately, or after a short period of shock and unconsciousness In less complete obstruction of the pulmonary circulation the clinical picture is that of acute cor pulmonale This is of sudden onset, the initial symptoms usually are dyspnea and severe pain These symptoms may appear simultaneously or dyspnea may precede by a short interval The pain is not unlike that of acute coronary occlusion and may be described as deep, crushing and constricting The patient is usually cyanotic and sweats profusely The pulse is rapid and the blood pressure is low Dilatation and pulsation of the veins

in the neck may be visible A forceful systolic impact may be heard in the
region of the pulmonary conus The pulmonic second sound is accentu
ated, there may be a systolic murmur and gallop rhythm and rarely a
friction rub may be noted over the region of the pulmonary conus

A much less dramatic picture is produced by smaller emboli and the
signs and symptoms are those of pulmonary infarction Often the only
inkling of a small embolus may be a sense of apprehension and anxiety
associated with palpitation and dyspnea In congestive heart failure pul
monary infarction may be masked by the passive venous congestion in
the lungs, and it is well to bear in mind the dictum of White that pul
monary embolism should be suspected in any patient who has congestive
failure with fever or in any patient who fails to respond to treatment in
the expected manner Pleural pain, which is usually of sudden onset, is
the cardinal symptom of pulmonary infarction The triad of pleural pain,
hemoptysis and a friction rub is almost diagnostic Unfortunately, this
triad is incomplete in the great majority of cases Unless there is hemop
tysis which characteristically consists of small amounts of light or dark,
almost pure blood, cough is usually not a prominent symptom Dyspnea
is usually not severe unless there is pleural pain

About twelve hours after the attack elevation of temperature begins
and progresses in steplike fashion to reach a peak of 101° to 102.5° F
on the second or third day, then the temperature declines in similar fash
ion This episode is attended by tachycardia and tachypnea which are
out of proportion to the degree of fever Not infrequently a low grade
daily elevation of temperature will be noted for several days prior to the
embolism This is considered to be evidence of venous thrombosis, and
when a patient who is a fit subject for thrombo embolism has such a
fever, a careful search should be conducted for this complication There
may be moderate leukocytosis after pulmonary infarction, the leukocyte
count, however, rarely exceeds 20,000 per cubic millimeter of blood
Jaundice is a rare complication of pulmonary infarction and usually oc
curs only in the presence of chronic passive congestion of the liver

With the exception of a pleural friction rub and the signs of pleural
effusion, pulmonary infarction produces no characteristic physical signs
The general poor condition of these patients frequently precludes ade-
quate examination Indeed, if there is good reason to suspect that pul
monary embolism has occurred, it is wise to confine the examination to
those parts of the chest which can be reached without moving the pa
tient The practice of having patients breathe deeply during the auscula

tory examination is to be condemned, since it is reported that fatal emboli have occurred during such activity Caution also must be exercised in palpation of the extremities in the detection of thrombosis, since vigorous squeezing of the calf muscles may dislodge an embolus

The Electrocardiogram in Pulmonary Embolism

The electrocardiographic changes in pulmonary embolism are those of acute cor pulmonale Observers are divided in their opinion as to the manner by which the changes are produced, and two possible

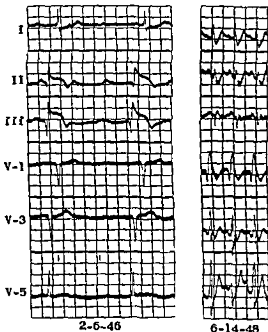


Fig 1 Comparison of electrocardiographic patterns in two cases *a* February 6 1946 acute posterior myocardial infarction *b* June 14 1948 pulmonary embolism Both tracings show deep Q_3 but the resemblance stops there

mechanisms have been advanced (1) acute strain of the right ventricle and (2) acute coronary insufficiency, due either to reflex vasoconstriction, or indirectly to shock and asphyxia Regardless of the exact mode of production, *it is agreed that electrocardiographic changes are not to be* expected unless there is relatively massive occlusion of the pulmonary artery (probably more than 50 per cent occlusion) When it is recalled that emboli of such magnitude are usually fatal it is easy to understand

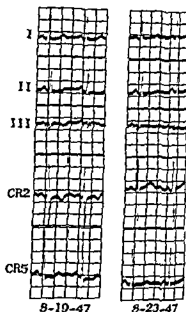


Fig 2 Electrocardiograms demonstrating the transitory nature of the changes in a case in which pulmonary embolism occurred August 18 1947 The important abnormality in this case is the inverted T wave in lead CR_2 which was present on August 19 and 20 (tracing not shown) but had disappeared by August 23 1947

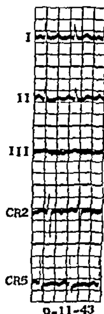


Fig 3 Electrocardiograms in a case of pulmonary embolism These tracings demonstrate the necessity of precordial leads since the changes are confined to the T waves in lead CR_2 which are inverted The T waves in lead CR_5 have remained upright

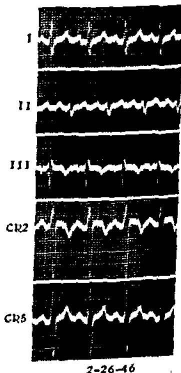


Fig 4 *Electrocardiogram obtained* one day after pulmonary embolism A prominent S wave is present in lead I and inversion of the T wave in lead III but the important change is the *inverted T wave in* lead CR_2

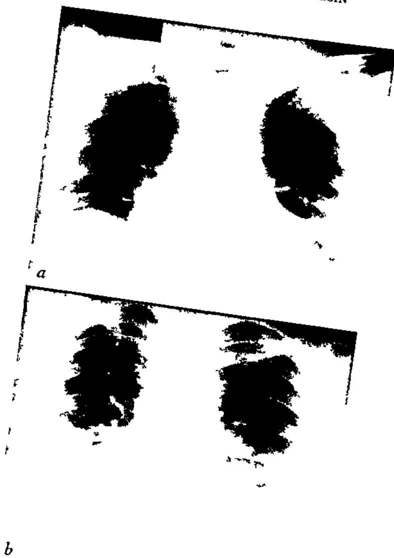


Fig. 5 The roentgen appearance of pulmonary embolism. *a* The enlargement of hilar vessels is more apparent on the right *b* In this subsequent roentgenogram the hilar vessels are no longer prominent and an infarct has appeared in the lower part of the right lung

why the electrocardiogram gives negative results in such a large proportion of nonfatal pulmonary emboli

Pulmonary embolism may produce various arrhythmias and disturbances of atrioventricular conduction, but the characteristic changes are confined to the ventricular complexes In the standard leads the

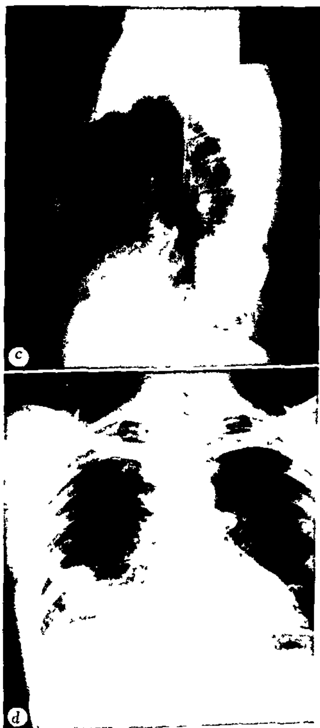


Fig 6 Pulmonary embolism The hilar vessels are enlarged and the peripheral pulmonary fields are clear except for diffuse haziness over the right which appears to be due to acute pleural effusion

Q_3T_3 pattern of posterior myocardial infarction may appear with certain important variations The S wave in lead I is deep and wide This may be so pronounced as to produce the picture of right bundle branch block (Fig 1) There is usually no Q wave in lead II, and if this deflection is present, it is inconspicuous The ST segment in lead II takes off below the iso-electric line and ascends in a gradual "staircase" fashion to the T wave which may vary from upright to diphasic, but rarely shows frank inversion The electrocardiographic changes of pulmonary embolism are



Fig 7 Acute pulmonary embolism with subsequent infarct on *a* September 8 1947 *b* and *c* September 17 1947 *c* illustrates the value of lateral views in the better defining of these lesions *d* September 23 1947 See page 512 for Figs *c* and *d*



Figs 7 c and d

transitory, and the tracing usually reverts to normal in a matter of hours or days (Fig 2) Serial tracings are valuable in distinguishing this from acute myocardial infarction, in which the changes persist for weeks or months The Q_3 pattern of myocardial infarction is often permanent

Precordial tracings are of even greater value than the standard leads, since they often show characteristic deflections when the standard leads are normal The changes are limited to those leads taken over the right side of the heart (position C_2) and consist of inversion of the T wave (Figs 3 and 4) In posterior myocardial infarction no such inversion occurs (Fig 1) The T wave inversion of anterior myocardial infarction may be distinguished from that of pulmonary embolism by its presence in several precordial leads particularly those taken in positions C_4 and C This emphasizes the importance of multiple precordial leads The practice of making a single lead and calling it lead IV is to be de plored

In pulmonary embolism the Q wave is insignificant or absent in lead ι V_F whereas in posterior myocardial infarction the Q wave is a promi nent deflection in this lead

Roentgenologic Findings in Pulmonary Embolism and Infarction

Roentgenologic examination may be very helpful in supporting or even making a diagnosis of pulmonary embolism or infarction, though too much reliance must not be placed on it Not infrequently the roent genologic examination gives negative results and in these instances it is of no value from the standpoint of exclusion One of the greatest ob stacles to roentgenologic diagnosis is the poor condition of the patient which precludes adequate examination Portable technic often complete ly obscures a lesion which could be readily identified in roentgenograms made with conventional target film distances and short exposure times In numerous articles attention has been called to the value of lateral, oblique roentgenograms and roentgenoscopic examination in detect ing lesions not visible in the posteroanterior (P A) projection Such procedures require special equipment and although their value to the roentgenologist cannot be denied the ultimate effect on the patient should be assessed before they are attempted

Recognition of pulmonary embolism from roentgenograms of the thorax depends on the alterations in the vascular pattern The hilar shadows and pulmonary vessels usually are accentuated on both sides





(Figs 5 and 6) This accentuation is confined to the central portion, peripherally the vascular shadows are diminished This picture is analagous to that of peripheral vasospasm and pulmonary hypertension observed by de Takats in experimental embolism In our experience, when these changes are evident in the roentgenogram, the entire vascular pattern is altered Westermark has described a similar picture of "anemic lung" involving individual pulmonary segments

The roentgenographic appearance of pulmonary infarcts varies In our experience the roentgenologic diagnosis of pulmonary embolism is more reliable than that of pulmonary infarction, which simulates other lesions Infarcts are peripheral, though this may not be evident in the posteroanterior (P A) view The size and shape of the shadow is dependent on the portion of the lung involved, and they may be triangular, round, oval or irregular It is important to note that the triangular shadow is the exception Hampton and Castleman have shown that even when the shadow is triangular, the apex usually points away from the hilus In the opinion of the same authors the medial or cardiac margin of an infarct is characteristically rounded or hump shaped (Figs 7 and 8) Small infarcts produce shadows which simulate pleural thickening rather than areas of consolidation

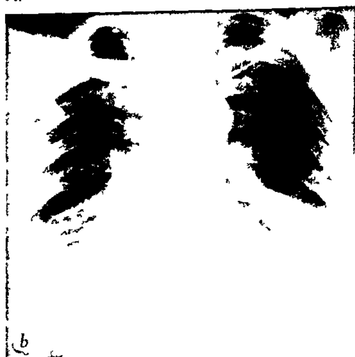
Since pulmonary infarcts are frequently multiple, the appearance of several shadows in the pulmonary fields should make the roentgenologist suspect infarction Serial roentgenograms are often useful in distinguishing pulmonary infarcts from other lesions There may be a delay of several days between the onset of symptoms and the appearance of the shadow (Fig 9) So-called incomplete infarctions heal by resolution and disappear in two to four days When necrosis has occurred, the shadow slowly decreases in size over a period of several weeks With infarcts of any size the end result is an area of localized or linear fibrosis with pleural thickening (Figs 10 and 11) Cavitation in a pulmonary infarct is evidence of formation of an abscess (Fig 12)

Acute pleural effusion frequently is present in pulmonary embolism or infarction or both and will obscure any intrapulmonary lesion The frequent occurrence of chronic passive congestion renders the roentgen-



Fig 8 Pulmonary embolism with infarction *a* April 3 1948, an indefinite lesion may be seen in the left costophrenic angle with plural reaction *b* April 10 1948 the infarct is clearly visible as a solid shadow with a rounded medial border There appears to have been involvment on the right between the two roentgenograms


a


b

ologic detection of infarcts difficult Elevation of the diaphragm on the affected side may be the only evidence of change on the roentgenograms and is of no diagnostic value since it is present in acute pleurisy of any type and frequently follows operations in the abdomen



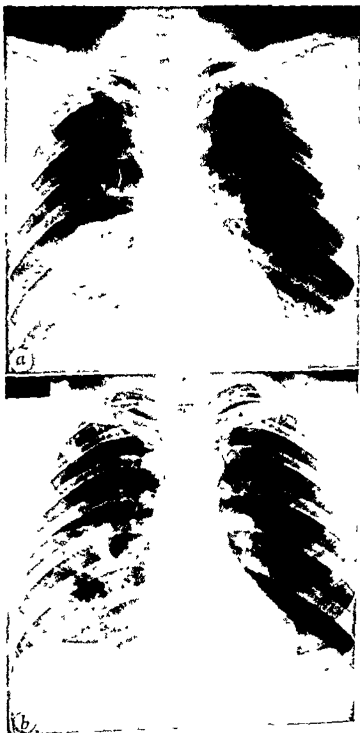
Fig 10 Healed pulmonary infarct represented by linear shadow with oval shadow at its periphrey

Differential Diagnosis

ACUTE MYOCARDIAL INFARCTION The symptoms of pulmonary embolism are frequently indistinguishable from those of coronary occlusion The circumstances preceding the acute episode may be of aid in differentiation A recent operation or accident, the presence of thrombophlebitis or the history of phlebitis in the past favors the possibility of pulmonary embolism An antecedent history of angina pectoris should suggest that the acute episode is myocardial infarction As a rule, dyspnea is the initial symptom of pulmonary embolism, whereas myocardial infarction



Fig 9 Acute pulmonary embolism. *a* June 1, 1947, roentgenogram made within twenty four hours of acute pulmonary embolism There may be enlargement of the hilar vessels on the left and there is an indefinite shadow in the left lower lung field *b* June 17, 1947, organization of infarct may be noted


a
b

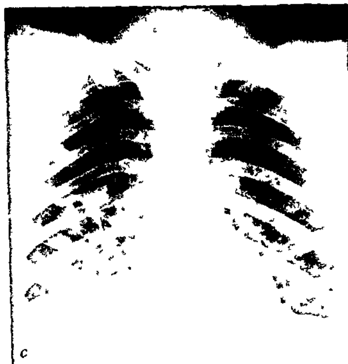


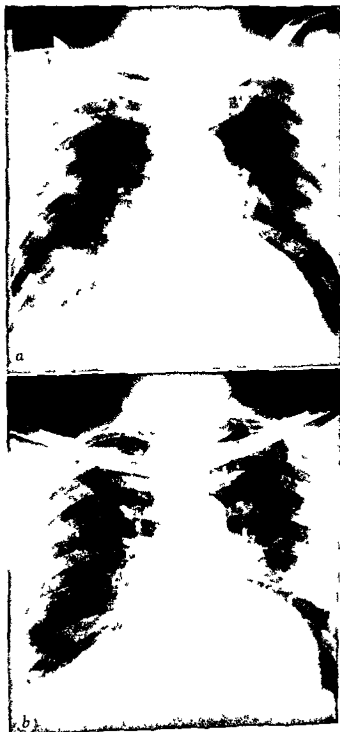
Fig 11 c

usually produces pain as its first manifestation Pulmonary embolism may recur several times in a period of weeks, an unusual happening in myocardial infarction The physical signs of acute cor pulmonale may give a clue to the correct diagnosis The presence of a friction rub over the conus arteriosus, however, will be a source of confusion The electrocardiogram is frequently helpful in distinguishing the two conditions,

emergency measures have been instituted, it is possible to await subsequent developments which may establish the diagnosis It is imperative that the correct diagnosis be made eventually, since the future management and ultimate prognosis are entirely different

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Fig 11 Large pulmonary infarct with subsequent organization and residual pleural thickening a, September 23, 1947 b, October 3 1947 c October 10, 1947


a
b

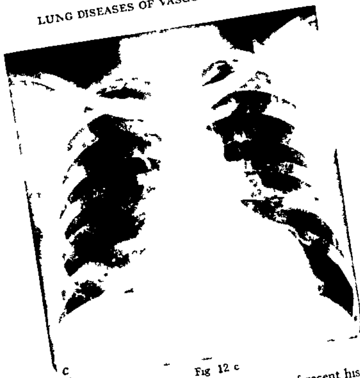


Fig 12 c

POSTOPERATIVE PNEUMONIA Again a knowledge of recent history of the patient is often of value in the diagnosis In pneumonia there may be a history of a preoperative upper respiratory infection A review of the operative procedure if one has been performed may indicate that the patient aspirated vomitus during anesthesia Pneumonia tends to occur early in the postoperative course and practically never happens after the patient has recovered from the operation and is out of bed Pneumonia tends to be insidious in its onset whereas pulmonary infarction is abrupt Cough is a prominent symptom of pneumonia the expectoration of mucopurulent sputum in pneumonia is unlike the frankly bloody expectoration of pulmonary infarction Pneumonia may be accompanied by a high septic type of fever and a leukocyte count of more than 20 000 whereas these are unusual in pulmonary infarction The two conditions

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Fig 12 Ser al roentgenograms demonstrat ng b lateral infarcts with healing on the r ght and abscess format on on the left *a* D cember 17 1947 *b* December 22 1947 *c* January 5 1948

cannot be distinguished by physical signs and except in the presence of acute cor pulmonale the roentgenogram and electrocardiogram usually give little help

Postoperative Bronchial Obstruction with Pulmonary Segmental Collapse Like pneumonia, bronchial obstruction is a complication of the early postoperative period, and is insidious in its onset The signs and symptoms may be the same as those of pulmonary infarction If the patient coughs, there is usually a clearly audible rattle as evidence of retained bronchopulmonary secretions When a large bronchus is completely obstructed, the roentgenogram will demonstrate loss of volume of the affected portion of the lung

Congestive Heart Failure with Acute Pulmonary Edema The lack of any evidence of serious heart disease usually will suffice to exclude pulmonary edema secondary to cardiac failure from pulmonary embolism Pulmonary embolism complicating pulmonary edema is often very difficult to diagnose, and frequently is a surprise at necropsy White emphasized that pulmonary embolism should be strongly suspected whenever a patient who has congestive cardiac failure has a fever or fails to respond to treatment in the expected manner

Pulmonary Tumors The roentgenographic appearance of pulmonary infarcts occasionally resembles that of pulmonary tumors, and we know of one case of pulmonary infarction in which cells found in the sputum were interpreted as carcinomatous cells Recent infarcts should give no difficulty in this respect, since serial roentgenograms will reveal a progressive decrease in the size of the shadow

Miscellaneous Conditions Other conditions which may simulate pulmonary embolism or infarction are spontaneous pneumothorax dissecting aortic aneurysm pulmonary abscess and interlobar effusion These require no special consideration as they are excluded rather easily or are of rare occurrence

Treatment of Pulmonary Embolism

Through the introduction of anticoagulant therapy and venous ligation in the treatment of thrombo embolism, the physician has been liberated from his former unhappy position of the helpless witness to a tragedy It can be categorically stated that the great majority of deaths from pulmonary embolism are preventable with the weapons which we now possess No attempt will be made to settle or even analyze the relative merits of venous ligation and treatment with anticoagulants

Our experience has been largely limited to the latter, and since we have found anticoagulants to be satisfactory, the major portion of this discussion will deal with the use of anticoagulants Venous ligation and anticoagulants should not be viewed as competitive measures, but as complementary procedures It has been our practice to reserve venous ligation for use in those cases in which administration of anticoagulants is contraindicated

The rationale of anticoagulant therapy is based on the proposition that only the freshly formed, propagating head of a thrombus is a potential embolus Attention has been called previously to the resemblance of this portion to an ordinary clot If the normal mechanism of coagulation can be interrupted, this proximal propagation of the thrombus with subsequent embolism cannot occur So far as the thrombus already present is concerned, there is evidence to indicate that it is no longer a potential embolus a few hours after its formation

ANTICOAGULANTS At present two anticoagulant preparations are available for clinical use heparin and dicumarol (3,3' methylenebis [4 hydroxycoumarin]) Although both of these substances are useful in the prevention of intravascular clotting, neither meets all the requirements of the ideal anticoagulant The advantages and disadvantages of each are listed in *Table I* It must be borne in mind that hemorrhage may result from the administration of either of these substances

Heparin represents a class of complex carbohydrate derivatives, small amounts of which are present in the circulating blood The manner by which it inhibits the coagulation of blood is complex and it requires the presence of a cofactor (heparin complement or pro antithrombin) which is supplied by the serum albumin Heparin prevents the clotting of fibrinogen by thrombin The conversion of prothrombin to thrombin is blocked by heparin There is experimental evidence to indicate that thrombi of recent formation disappear with the use of heparin The intravenous injection of 50 mg of heparin in man produces prolongation of the coagulation time to about four times the normal for a period of one hour, after which the coagulation time slowly returns to normal within three hours By incorporating heparin in a slowly absorbed medium (Pitkin menstruum) the effect of a single intramuscular or subcutaneous injection may be sustained for two or three days

Impaired coagulability of the blood does not appear until two or three days after the first dose of dicumarol, and the effect does not disappear until two to four days after the last dose Dicumarol interferes

with clotting of the blood by lowering the level of prothrombin in the plasma The mode of action is unknown, though the evidence indicates that dicumarol suppresses the formation of prothrombin It has been suggested that this effect is produced through the action of dicumarol as a specific antagonist to vitamin K

Administration of Heparin If it is desirable to give heparin for a period of one or two weeks, the continuous intravenous method is the procedure of choice Two hundred milligrams of concentrated heparin is added to 1,000 cc of physiologic saline solution or 5 per cent solution of dextrose Administration is begun at a rate of 25 drops per minute It is necessary to determine the coagulation time at intervals of four hours for the first twelve hours and at intervals of twelve hours thereafter The rate of flow is then adjusted in order to keep the coagulation time between fifteen and twenty five minutes (Lee White method) If bleed ing occurs the drip is stopped and the coagulation time will return to normal within one hour

When the effect of heparin is required for only a few days, the intermittent intravenous administration of the concentrated (stock) solution is effective and much simpler Doses of 50 mg are given every four hours Determinations of the coagulation time are unnecessary with this method If bleeding occurs the effect of heparin will disappear in less than three hours after the last injection

The intravenous administration of 50 mg of protamine sulphate will promptly neutralize the effect of 50 mg of heparin This may be used if major hemorrhage threatens Since it may have a toxic effect, protamine sulphate must be given slowly

There are reports of suitability of heparin incorporated in a slowly absorbed medium (heparin in Pitkin's menstruum) In our experience the injections are too painful, though others have been able to control the pain A single injection of this preparation may produce prolonged coagulation time for periods of two to three days This effect, however, is variable and unpredictable If bleeding occurs, one has no control over the coagulation time, and protamine sulphate has only a transitory effect for 35 to 45 minutes after which the coagulation time returns to its pre viously high level

Administration of Dicumarol It has been emphasized by numerous writers that the administration of dicumarol must be based on the level of prothrombin in the blood Dicumarol should never be given unless reliable determinations of prothrombin can be made To give too little

dicumarol is useless, to give too much is dangerous It is unfortunate that it has become the practice to report prothrombin time, rather than the prothrombin level in percentage of normal Whatever the method of reporting the results, the physician should become familiar with the prothrombin time in his laboratory for three critical values, 30 per cent, 20 per cent, and 10 per cent normal prothrombin activity Reasonably accurate prothrombin times for these values can be determined for 30 per cent, 20 per cent and 10 per cent dilutions of normal plasma in 0 9 per cent solution of sodium chloride These times will vary with the thromboplastin used in the determinations but the laboratory consultant will be able to furnish the required conversions

During administration of dicumarol the prothrombin level should be kept between 30 and 10 per cent of normal Thrombosis rarely occurs when the prothrombin level is less than 30 per cent of normal and bleeding is rare if the percentage of prothrombin is higher than 10 per cent of normal We have followed the method of administration of dicumarol developed by Allen, Barker and their associates The entire amount for one day is given in a single oral dose in the afternoon Except for the first two days, the size of the dose depends on the prothrombin level in the blood drawn that morning On the first day 300 mg is given Thereafter, the usual plan is to administer 100 mg on those days that the prothrombin level is higher than 20 per cent of normal, and none if it is less than 20 per cent Minor variations are necessary of course with individual patients Some persons are resistant to dicumarol and daily doses of 200 or even 300 mg are required to obtain the desired effect on the concentration of prothrombin The general trend of the prothrombin level must be taken into consideration in judging the dose. Thus if the concentration is decreasing rapidly, but is still more than 20 per cent the dose of dicumarol for that day is omitted If the concentration of prothrombin is rising rapidly, but is still less than 20 per cent 100 mg is given Administration of dicumarol should be continued until the patient has been ambulatory for three to seven days

If the level of prothrombin is lowered excessively or bleeding occurs, use of vitamin K is effective in elevating the prothrombin levels If the prothrombin value remains less than 10 per cent for two successive days, 36 mg of menadione bisulfate should be given intravenously If major hemorrhage develops, 72 mg of menadione is given every eight hours along with transfusions of fresh citrated blood until bleeding stops In

cases of minor bleeding it is usually sufficient to stop the administration of dicumarol and await further developments

COMBINED USE OF HEPARIN AND DICUMAROL In most cases of thrombo-embolism dicumarol will be the agent of choice since treatment will be prolonged To achieve an anticoagulant effect during the period of delay of dicumarol the simultaneous use of heparin and dicumarol has proved effective This is achieved by giving dicumarol as described Heparin is given by the intermittent intravenous method and discontinued when the prothrombin level is less than 20 per cent While heparin is being given blood for determinations of prothrombin must be drawn at least three and a half hours after a dose of heparin

INDICATIONS FOR ANTICOAGULANT THERAPY The combined administra tion of heparin and dicumarol should be started immediately in any case of nonfatal pulmonary embolism or peripheral venous thrombosis unless a definite contraindication for such therapy exists

In addition to its use after thrombosis or embolism has occurred dicumarol is effective as a preventive measure for certain types of pa tients who are particularly susceptible to thrombo embolism It has been shown that the likelihood of postoperative thrombosis and embolism is increased tenfold in patients who have had such an accident following previous operations On this basis it is usually our practice to start the administration of dicumarol 48 hours after the operation and continue its administration until the patient is dismissed from the hospital

Since operations on the lower part of the abdomen carry a high in cidence of thrombo embolism dicumarol is given in the same manner to such patients if two or more of the following conditions exist old age, obesity, infection malignant disease heart disease varicose veins anemia or polycythemia vera Treatment with dicumarol is indicated in fractures of the hip De Takats has devised the heparin tolerance test to detect a tendency to thrombo embolism and has stated that hyporeactors are candidates for anticoagulant therapy Although a laboratory procedure of this type is very desirable there is insufficient evidence to support the usefulness of the heparin tolerance tests In addition the test is time consuming and a simpler procedure would be more useful

Evidence is accumulating that dicumarol is of value in the prevention of pulmonary embolism in certain nonoperative conditions notably acute myocardial infarction Most authors who have investigated the subject have expressed the opinion that dicumarol should be given routinely from the onset in these cases and its use continued until the

patient is permitted to be out of bed The use of anticoagulants in myocardial infarction has been objected to by some on the grounds that it may increase the hemorrhage into the infarct That this objection is invalid has been shown by the experimental work of Beattie and his associates and Blumgart They found no difference in the experimental infarcts of control animals and those treated with dicumarol

Anticoagulant therapy is unnecessary in uncomplicated cases of congestive heart failure which responds rapidly to ordinary therapeutic measures Its use is indicated in those cases in which the condition is refractory, or in which episodes of thrombo embolism have occurred

In the rare cases of idiopathic recurrent thrombosis and embolism dicumarol may be given indefinitely with the strict provision that the concentration of prothrombin be determined at least once a week This should be preceded by a period of closely supervised control of dosage in order to develop a pattern for the individual patient As a rule, however, bilateral ligation of veins is a preferable procedure and recourse to dicumarol therapy should be made only after interruption of the veins has failed

CONTRAINDICATIONS TO ANTICOAGULANT THERAPY Dicumarol should never be used in the following conditions (1) renal insufficiency with retention of nitrogen, (2) hepatic insufficiency, (3) purpura of any type, (4) blood dyscrasias which produce a tendency to bleeding (5) subacute bacterial endocarditis, and (6) after operations on the brain or spinal cord

Dicumarol should be used with extreme caution in the following (1) active peptic ulcer, (2) open granulating wounds, other ulcerations and potentially bleeding surfaces, (3) in the presence of drainage tubes in body orifices or surgical wounds, and (4) severe dietary or vitamin deficiencies

The same contraindications apply to heparin as to dicumarol with the exception that heparin may be used in the presence of hepatic or renal insufficiency

VENOUS LIGATION The indications for venous ligation are similar to those for anticoagulant therapy although we reserve this procedure for use in those cases in which anticoagulant therapy is contraindicated So far as venous ligation itself is concerned, there appears to be no contraindication to it provided that the patient's general condition will permit an operative procedure If interruption of veins is to be undertaken it should be bilateral and must be proximal to the thrombus

Surgeons disagree about the proper site of ligation Though it causes more edema Homans has stated that he prefers to ligate the common femoral vein since it affords more protection and White has recommended this site in medical patients with thrombo embolism Allen has found ligation of the superficial femoral vein with aspiration of the proximal clot to afford satisfactory protection and less edema occurs Ligation of the iliac veins or the inferior vena cava is a major surgical procedure requiring general anesthesia and is rarely indicated Many authors have recommended the use of anticoagulants for a few days after ligation of the vein to prevent thrombosis in the proximal segment of the vein

TREATMENT OF ACUTE PULMONARY EMBOLISM After a small pulmonary embolism or infarction in which there is no evidence of shock or cardiac embarrassment no treatment is required except the use of anticoagulants to prevent successive fatal embolism In cases of large pulmonary embolism a few simple measures appear to have definite value in preventing the death of the patient These consist of (1) oxygen administered by mask intranasal catheter or in a tent (2) papaverine hydrochloride *(0 64 gm) given intravenously with one repetition of the dose* if necessary and (3) atropine sulfate (0 32 mg) given intravenously with one repetition of the dose if necessary

GENERAL MEASURES Although they are not as effective as the anticoagulants certain prophylactic measures must not be ignored particularly when anticoagulant therapy is contraindicated The present trend toward early ambulation for both postoperative and nonsurgical patients appears to be of some value if properly used though the most recent reports offer little encouragement Too often early ambulation has consisted of placing a weak patient in a chair and permitting him to sit immobile for a long period Obviously such a state favors stagnation of blood in the legs and the patient would be better off in bed until he can actually achieve the state of ambulation The practice of dangling is to be discouraged for elderly patients Attempts to improve the circulation should begin as soon as the patient has recovered from the acute effects of the operation Bandages on the legs massage and passive motion are of value but if the patient is able he should be encouraged to move his lower extremities *Whatever means one may wish to employ to obtain this end* is of little consequence so long as the patient moves his legs a thousand times a day

Other postoperative measures designed to improve the circulation

include the avoidance of Fowler s position, frequent turning of the patient, encouragement of deep breathing and coughing adequate hydration and the avoidance of tight dressings and binders

Since cholinergic drugs have been shown to have a favorable effect on restoration of shortened coagulation times to normal, de Takats has recommended that neostigmine be given to all patients immediately after operations It is his practice to give 1 0 cc of 1 1,000 solution at intervals of four hours until ten doses have been given

Prior to operation it is obvious that attention must be given to the general condition of the patient Cardiac compensation should be as complete as can be obtained Digitalis has incurred disfavor with some clinicians because it increases coagulability of the blood It seems doubtful that this effect would be sufficient to outweigh the benefit which digitalis gives to a failing heart

Elective surgical procedures on obese patients should be delayed until suitable reduction of weight has been accomplished Major varicose veins should be obliterated before any major operation, any anemia should be corrected The use of tobacco should be prohibited for several days before any operation and until the patient is out of bed

TABLE I

COMPARISON OF ANTICOAGULANTS (from Allen)

I Heparin
 A Advantages
  1 Quick effect on the blood
  2 Quick disappearance of the effect on the blood
  3 Can be administered without laboratory control
 B Disadvantages
  1 Expensive *
  2 Need for parenteral administration
II Dicumarol
 A Advantages
  1 Inexpensive *
  2 Effective orally
 B Disadvantages
  1 Effect on the blood is delayed
  2 Effect on the blood persists for days after the cessation of administration

3 Daily determination of prothrombin time necessary for efficient and safe administration

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*Heparin injected intravenously in amounts of 50 mg every four hours currently costs about $9 00 a day Enough dicumarol to produce the desired effect on the blood costs only a few cents each day

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PULMONARY EDEMA

By Andrew L. Banyai, M D and J Winthrop Peabody, M D

This is a common condition that may occur at any age period The term implies the collection and accumulation of a low protein ultra filtrate of blood plasma in the alveoli, bronchioles and bronchi and also, in the interstitial spaces of the lung The edema fluid contains the the same electrolytes and nonelectrolytes as the plasma and about in the same concentration Passage of this fluid from the capillaries is brought about by the following factors

1 Increased permeability of the wall of the capillaries
2 Increased blood pressure in the pulmonary vessels
3 Dilatation of the pulmonary blood vessels
4 Lowered colloidal osmotic pressure of the blood plasma
5 Decrease in the lymphatic drainage of the lung

These changes may result from a great variety of pathologic conditions which act singly or collectively Clinically, several entities are recognized as possible causative factors of pulmonary edema These are

1 Anoxia
2 Inflammatory pulmonary changes
3 Mechanical influences
4 Toxic agents
5 Anaphylactic and allergic states
6 Increased negativity of the intrapleural pressure
7 Reflex causes
8 Hypoproteinemia
9 Endocrine imbalance
10 Miscellaneous factors

Anoxia develops in consequence of heart failure, shock, extensive loss of lung parenchyma due to pathologic alterations in the pulmonary tissue or in the pleura, or blood loss. Heart failure exerts a complex influence upon the oxygen carbon dioxide exchange of the lung Lack of sufficient oxygen intake increases the body s sensitivity to respiratory stimuli Consequently, respirations become deeper This, in turn implies increased negativity of the intrapleural pressure The more negative the intrapleural pressure the more blood is drawn to the chest from other parts of the body The consequent increased filling of the right ventricle makes a greater filling of the pulmonary vessels possible

Hyperventilation entails the risk of increased elimination of carbon

dioxide from the alveoli Consequently, the carbon dioxide content of the blood is reduced and thus, normal stimulation of the respiratory center will be lacking This, in turn, results in rapid, shallow respiration The latter causes added anoxia on account of the insufficiency of the pulmonary air current Another harmful effect of undue loss of carbon dioxide is a decreased dissociation of oxyhemoglobin, that is, an increased attachment of oxygen to the hemoglobin Pulmonary edema itself contributes to oxygen deficiency and to excessive loss of carbon dioxide on account of the latter's solubility and diffusibility in water, as compared with that of oxygen

Recumbency in heart failure in the form of bed rest is likely to result in increased venous return to the chest which may be followed by pulmonary congestion and edema Overt or latent peripheral edema often disappears on bed rest, but at the same time, evidence of pulmonary edema develops The cardiac patient so treated derives from this well meant medical intervention nothing but harmful "benefits" In these patients, an angiotropic movement of fluids takes place, that is, from tissue spaces to the blood capillaries Such influx of fluids causes hemodilution increased blood volume and increased venous pressure In this connection, it is worth quoting the remarks of Kerr

> "The posture of the patient with dependent edema or anasarca is of great importance It is better to put the edematous and orthopneic patient in a comfortable chair with support for the shoulder girdle than to force him to remain in a cramped position in bed SOGGY FEET ARE BETTER THAN SOGGY LUNGS"

Also, in heart failure slowing of the circulation favors anoxia Baasch thought that heart failure led to pulmonary decompensation and thus, to anoxia in two possible ways

1 By distention and stiffening of the lung capillaries, which interfere with the respiratory motion of the alveoli (expansion and contraction)

2 By an inward swelling of the capillaries, which reduces the alveolar surface area

It is a well established fact that hypoxemia increases the permeability of the wall of the capillaries Particular emphasis on this point was given by Drinker who said that

> "of factors leading to edema, increased permeability of the lung capillaries is by far the most important, and of all the

possibilities for inducing it. Anoxia is decidedly the most frequent.

Pulmonary edema of any cause creates a vicious circle. By the obliteration of numerous alveoli, it leads to hypoxemia which, in turn, increases vascular permeability, with consequent added formation of pulmonary edema. Increased capillary permeability permits the diapedesis of plasma proteins from the capillaries. In this fashion, substantial loss of plasma protein may take place. Thus, a second vicious circle is set up. Loss of plasma protein means reduction in its colloidal osmotic pressure. Such reduction augments the formation of edema. Two other factors which contribute to the formation of edema in the lung are

1. Elevation of the pulmonary venous pressure.
2. Inefficiency of pulmonary lymphatic drainage.

Landis demonstrated that filtration of fluids from the capillaries was directly proportionate to the increase in the venous pressure. Drinker called attention to the inadequacy of pulmonary lymphatic drainage in general. In patients with heart failure its competency is even less satisfactory on account of the high venous pressure which obviates the free centripetal flow of lymph.

The serious consequences of shock include lessened respiratory function and consequent hypoxemia. As pointed out before hypoxia causes increased permeability of walls of capillaries. Pulmonary edema has been observed in patients with insulin shock.

Extensive loss of the lung parenchyma occurs in a number of acute and chronic pulmonary ailments. The consequent inadequacy of oxygen intake forces the heart to drive larger amounts of blood through the lung so as to provide sufficient oxygen for the body tissues. In this manner, a rise in the pressure in the pulmonary capillaries is inevitable. Such increased intravascular pressure is bound to end in pulmonary edema.

Effect of arterial blood loss on the development of pulmonary edema was studied experimentally by Eaton and his associates (1945). They found that pulmonary moisture was increased during the first 20 minutes after the removal of 25 per cent of the blood volume of the animal, decreased below the normal during the next 20 minutes, again elevated during the third 20 minutes period, and then gradually returned to normal. Following a fall in the pulmonary arterial and peripheral venous pressure during the first 20 to 40 minutes, there is

a subsequent rise during the next 30 minutes which is followed by stabilization at a level lower than normal Pulmonary edema detectable during the second half hour is attributed to acute hypoxia of the body The latter is the first result of loss of blood volume and erythrocytes

Inflammatory changes in the lung as well as severe systemic infection may be responsible for pulmonary edema The latter is known to occur in communicable exanthematous diseases of childhood, also in influenza, pneumonia, typhoid fever and others In exanthematous diseases the appearance of pulmonary edema either coincides with the height of toxic symptoms, or it follows the latter several days later Its onset is thought to be due to an increased permeability of the capillaries or to anoxia, or both The same factors are operating in widespread lung diseases In severe systemic infections, increased permeability of the pulmonary capillaries is the causative factor

Pulmonary edema develops immediately, or may be delayed as much as twelve hours following exposure to toxic fumes or noxious gases These include bromine, chlorine fluorine, ammonia, arsenious chloride, hydrogen bromide hydrogen chloride, hydrogen fluoride, oxides of nitrogen phosphorous oxychloride, phosphorous trichloride phosphorous pentacholoride phosphorous pentoxide, methyl bromide sulfur dioxide, phosgene, diphosgene, chloropicrin, cadmium, nickel carbonyl iron carbonyl and dusts of certain alkaloids Pulmonary changes caused by these chemicals and substance and their treatment are discussed in detail under the respective headings

Mechanical factors have an important role in the causation of pulmonary edema in patients with heart failure Since the experimental work of Welch (1898), it has been known that failure of the left ventricle of the heart is bound to lead to pulmonary edema in the presence of a normally functioning right ventricle Under such circumstances disproportionately large volumes of blood are driven to the lung At the same time the removal of blood from the lung through the pulmonary vein to the left heart chambers is incomplete The consequence is a distention of and increased pressure in the pulmonary vessels Pulmonary edema may result from long standing mitral stenosis

Development of pulmonary edema through the action of toxic agents occurs in acute glomerulonephritis eclampsia, severe burns, severe systemic infections and in poisoning from the bite of Latrodec

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Development of pulmonary edema through the action of toxic agents occurs in acute glomerulonephritis, eclampsia, severe burns, severe systemic infections and in poisoning from the bite of Latrodec

tus mactans (black widow or shoe button spider) The latter is found widely in the United States No doubt, in these cases, damage to the pulmonary capillaries, with consequent increase in their permeability, is the principle causative factor

Lundy and his collaborators (1949) reviewing their experience with 6,616 blood transfusions, report on the occasional occurrence of pulmonary edema as a result of an allergic reaction or in consequence of overloading the circulatory system

Anaphylaxis as the cause of pulmonary edema has been seen following the administration of immune globulin for the prophylaxis of measles, also after the injection of immune serums given therapeutically Allergy to certain medicaments may have similar consequences We have seen pulmonary edema following the topical application of pontocaine prior to bronchoscopy, also, following intrabronchial instillation of iodized oil

Increased negativity of the intrapleural pressure with associated decrease in the intra alveolar pressure, can be brought about by various factors These include obstruction of the tracheobronchial tract by inflammatory changes aspirated foreign bodies and intrinsic or extrinsic, benign or malignant tumors, or by compression of major air passages by neighboring extraneous pathologic changes Other possible factors are laryngospasm, obstruction of the pharyngo-laryngeal lumen by other means, drowning, and rarely, rapid removal of large pleural effusion by aspiration Sudden, persistent, abnormal increase in the negativity of the intrapleural pressure represents a powerful suction force This causes a larger flow of venous blood from the periphery of the body to the right auricle From here, large amounts of venous blood reach the right ventricle and are driven to the lung This concept is supported by the observations of Shuler and his associates (1942) who demonstrated that during ordinary inspiration, with only slight increase in the negativity of the intrapleural pressure, there is an augmentation of the output of the right ventricle and a decrease of the output of the left ventricle The latter change is quite marked when there is a sudden, persistent abnormal increase in the intrapleural negative pressure The reason is that the return flow of blood from the lung to the left auricle is handicapped by the powerful suction of the negative intrapleural pressure Thus, large quantities of blood are bound to accumulate in the lung The intravascular pressure becomes greatly elevated and pulmonary edema follows Its develop-

ment is enhanced by the simultaneous retardation of lymphatic drainage from the lungs Investigative studies of Huggett (1924) revealed that inspiration against resistance increased the output of the right ventricle Drinker and Warren (1943) proved that forced, exaggerated respiration and reduced oxygen supply cause the formation of pulmonary transudate

Reflex pulmonary edema is one of the most puzzling clinical entities The reflex which elicits pulmonary edema may originate from the central nervous system, from thoracic or from thoraco abdominal trauma The former is represented by conditions such as spontaneous or traumatic intracranial hemorrhage, polyomyelitis, tabes and coma of any sort, including that due to encephalitis, meningitis, alcohol, overdose of barbiturates, general anesthesia and general toxicosis during severe infections and others Weismann noted that the maximum extent of pulmonary edema developed one hour after intracranial hemorrhage In case of coma when partial tracheobronchial obstruction is present, the consequent hypoxia and more negative intrapleural pressure are contributing substantially to the development of edema According to the experimental observations of Jarisch and his associates, certain types of central nervous system irritation produce sympathetic stimulation, with consequent peripheral vasoconstriction The latter forces the blood from the periphery of the body into the lesser circulation Simultaneously, due to stimulation of the sympathetic nerve supply of the lung, there is a loss of tonus of the pulmonary vessels These two factors bring about an over filling of the vascular bed of the lung and pulmonary edema Moreover it is well to keep in mind that renal function is frequently depressed in coma and hypoxia is usually present

Another form of reflex pulmonary edema is that encountered in patients with severe nonpenetrating injuries to the chest and with thoraco abdominal wounds without direct trauma to the lung In the former, it is assumed that three causative factors are responsible for the edema, namely, restriction of respiratory excursions of the chest, bronchospasm and pulmonary vasodilatation The same mechanism is operative in thoraco abdominal injuries But in the latter, the role of limitation in the respiratory motions of the diaphragm is greater than in the former In both instances, however, reduced respiratory expansions of the lung are bound to cause various degrees of atelectasis Atelectasis is known to render the intrapleural pressure more negative

Development of atelectasis is produced by bronchial occlusion which is partly due to bronchospasm, partly to accumulation of bronchial secretions and/or inflammatory exudate Such accumulation is readily undestandable when one thinks of the patient s cough being spontaneously suppressed on account of pain *The suction effect of the* more negative intrapleural pressure causes an engorgement of the non atelectatic segments of the same lung Furthermore, it is well to remember that limited, subnormal respiratory excursions of the lung result in hypoxia which, in turn, increases capillary permeability of the pulmonary vessels Finally, massive atelectasis is bound to cause a shift in the position of the heart and large mediastinal blood vessels and thus it may lead to circulatory embarrassment, with further impairment of the respiratory gas exchange

Hypoproteinemia is the cause of pulmonary edema in certain cases of nephrosis and liver disease It is likely to be of significance in large arterial blood loss Loss of large amounts of blood proteins means a lowering of the colloidal osmotic pressure of the plasma This, in turn, according to well known principles of physics, leads to an outpour of plasma from the capillaries and thus to pulmonary edema

Cyclical pulmonary edema has been observed directly before and during menstruation It is reasonable to assume that in these individuals excessive production of progesterone and estrogen causes a decrease in the excretion of sodium Consequently, the plasma volume and blood pressure are increased and an increased infiltration of plasma takes place from the capillaries into the alveoli

Under miscellaneous causes of pulmonary edema, conditions will be discussed *the pathogenesis of which is reasonably certain* and also conditions where the causative factors are obscure To the first category belong penetrating wounds of the chest On the basis of their experiments, Gibbon and Gibbon (1942) state that edema encountered in thoracic surgery results from increase in the capillary blood pressure, decreased colloidal osmotic pressure of the blood plasma with a consequent increased capillary permeability Brewer and his associates, (1946) refer to the following early factors in the development of pulmonary edema

1 Exaggerated inspiratory efforts
2 Tracheo-bronchial obstruction
3 Anoxia

As stated previously, any of these factors is capable of causing pul

monary edema but anoxia should be considered the most potent one. Anoxia may be brought about by excessive blood loss, pulmonary changes associated with the loss of large respiratory surface areas, direct occlusion of the major air passages and shock.

With a clear understanding of the mechanics of the origin of pulmonary edema, one can appreciate that under certain conditions medical intervention may provoke it, for instance, by giving large infusions or by the administration of desoxycorticosterone acetate or progesterone.

Pulmonary edema has been observed in pregnancy, without cardiorenal disease. It may occur during induction of anesthesia or during prolonged labor. No plausible explanation is available as to its cause. Pulmonary edema may occur in beri beri and thyroid crisis. Also, cases are on record where pulmonary edema developed after the injection of adrenalin, chloral hydrate, morphine, muscarine and prostigmine. Cases are on record in which insulin shock therapy was followed by pulmonary edema.

Pathology

Pathologic findings show great variations corresponding to the etiology of pulmonary edema. In cases attributable to unilateral local factors, the lesion is limited to one lung and may be localized in a circumscribed area of it. In heart failure, following inhalation of noxious gases and fumes, and in conditions which affect the blood or the walls of the capillaries, pulmonary edema is bilateral. It may involve the entire extent of both lungs or its predominant location is the lower one half of this organ. In extensive pulmonary edema, post mortem examination reveals that the lung is larger and heavier than normal and it shows pitting. Large amount of foamy, watery fluid oozes out of the cut surface. It may be colorless, brown or red, depending upon the degree of congestion. The alveoli are filled with albuminous fluid. The presence of a few desquamated alveolar epithelial cells is also noted. Pulmonary edema represents a predilectional state to the invasion of pathogenic micro organisms. Consequently, bronchopneumonia, lobar pneumonia, severe tracheobronchitis and bronchiolitis may complicate the picture. Rigler emphasizes that in some cases the edema is intersitial rather than alveolar. Such a condition may be encountered as an early phase of an inflammatory process or in other types of pulmonary edema.

Symptomatology

Symptoms of this condition are predicated upon the type and extent of the edema. The usual manifestations of pronounced pulmonary edema are dyspnea that may be agonizing, tightness in the throat and chest, feeling of oppression, strangulation, asphyxiation, hacking or paroxysmal cough, expectoration of large amounts of colorless, occasionally pink, blood tinged, foamy sputum. When *coexistent infection* complicates the condition, chills and fever are complained of.

Diagnosis

Acute pulmonary edema causes considerable cyanosis. The latter may be seen all over the body in severe cases. In widespread pulmonary edema the patient is evidently in great respiratory distress and his skin bathed in cold sweat. The history of the case is of utmost importance, as to diagnosis as well as to the management of the patient. Inquiry should be made relative to possible causative factors enumerated in connection with the discussion of pathogenesis. In patients with heart failure the onset is usually sudden. Not infrequently, it takes place at night.

Physical findings are scant or entirely absent in localized forms of the disease. In more extensive, bilateral cases, impaired percussion note or dullness is found at both bases, together with large, bubbling rales over the same area. The latter is audible throughout both lungs in widespread edema. Hydrothorax may or may not be present.

Roentgenograms of the chest may reveal pulmonary edema before subjective symptoms and physical signs are noted. Typical roentgenologic findings are: Fine or coarse mottling, or mottled diffuse haziness, particularly in the central, middle and basal zones. The lateral outer region of the lung fields usually remains clear. The roentgenologic manifestations are, as a rule, bilateral and symmetrical. In rare instance, however, the lesion may be limited to one lobe or one lung. On the basis of roentgenologic findings, pulmonary edema should be differentiated from diseases casting *diffuse nodular shadows* on the film, such as miliary abscesses and tuberculosis, bronchiolitis, miliary bronchopneumonias, Bouillaud's disease, congenital miliary cystic disease, metastatic carcinoma, Hand Schueller Christian disease, sarcoidosis, Hodgkin's disease, berylliosis, schistosomiasis, tropical eosinophilia, syphilis, virus pneumonia and others. In pulmonary stasis with or without edema, one finds an enlargement of the hilar blood ves

sels giving a butterfly-shaped appearance to this area Clinically, one should consider and rule out pneumonia and other extensive infections of the lung, pulmonary infarction, bronchial asthma, spontaneous pneumothorax, angina pectoris and acute cor pulmonale resulting from sudden obstruction of the pulmonary circulation by massive emboli With reference to the latter White duly emphasized the following points of diagnostic importance

1 History of surgical intervention, fracture of long bones or recent phlebothrombosis

2 Sudden onset with dyspnea, ashen face, cold sweat, thready pulse and low blood pressure

3 Absence of abnormal physical findings over the lungs in the first 12 to 24 hours

4 No abnormal roentgenologic findings on early chest films, unless elevation of a hemidiaphragm is noted

5 Characteristic electrocardiographic changes

6 In severe cases, there is increased prominence and pulsation noticeable by inspection and palpation in the second and third intercostal spaces directly left of the sternum Also, there is friction rub in the same area The patient is cyanotic, has gallop rhythm and dilatation and pulsation of the jugular veins

Prognosis

The outcome of pulmonary edema is dependent upon its cause, extent, complications and in no small degree, upon the promptness and competency of therapeutic intervention In cardiac cases, the first attack may prove fatal If the patient recovers from the first attack, he is likely to have recurrences

Treatment

The most important measure in the treatment of this condition is the inhalation of 100 per cent oxygen under 6 cm water expiratory pressure Inhalations are started as soon as the diagnosis is established The cardinal role of the measure is well emphasized in the advice of Drinker who said

"The time to begin to use oxygen is before there is any certainty that it is needed "

Inhalations are given with the aid of a well fitting oronasal mask From 8 to 10 liters are delivered per minute until the patient is comfortable, then 6 liters per minute for one to two days The rationale of this

method is based on the manifold effect of oxygen inhaled and exhaled under positive pressure To begin with it directly counteracts anoxia and thereby reduces the permeability of the pulmonary capillaries The increased pressure mechanically dilates the lower air passages and thus renders them accessible for the free ingress and egress of atmospheric air Positive pressure inspiration and expiration lower the negativity of the intrapleural pressure Thus the excessive suction effect of the latter is lessened Consequently less blood *is driven by the right ventricle* to the lung, the return flow from the lung to the left auricle is facilitated and free drainage through the pulmonary lymphatics is aided *The high hydrostatic pressure is relieved in the pulmonary* capillaries and the permeability of the wall of the latter is restored to normal

Unless irreversible pathologic changes have taken place the response to this treatment is remarkable, indeed Although positive pressure inhalation during both respiratory cycles is the better method satisfactory therapeutic results follow when oxygen is given under positive pressure during the expiration phase only This is simpler of the two procedures According to the requirement of the individual case the pressure under which oxygen is administered may be reduced after the first 24 hours to 3 cm of water and still further reduced to 1 cm of water or to atmospheric pressure thereafter In patients whose condition is less serious it is expedient to give oxygen inhalation *under pressure* for two hours only and then continue inhalations without positive pressure

Barach observed excellent results from the inhalation of a mixture of helium and oxygen under 3 to 6 cm of water *expiratory pressure* Also he advocated the administration of 0 5 cc of 1 100 aerosolized solution of epinephrin to overcome coexistent bronchospasm and 0 5 to 1 cc of aerosolized 1 100 solution of neosynephrin for *vasoconstriction* so as to reduce bronchial mucosal swelling and widen the *bronchial lumen* Aminophyllin is a useful drug for inducing relaxation of spastic bronchial smooth muscles The usual effective dose is 7½ grains (0 5 Gm) intramuscularly, 3¾ grains (0 25 Gm) or 7½ grains (0 5 Gm) intravenously *It is mandatory to give intravenous* aminophyllin SLOWLY!

When tracheobronchial obstruction is suspected freeing *the air* passages *from* accumulated fluid is of paramount importance *This* can be carried out by bronchoscopic aspiration or by suction through

a tracheal catheter Unless this is done the oxygen inhaled may not gain access to the alveoli

Pulmonary edema can be prevented in persons who inhaled noxious fumes or gases in industrial plants These individuals are given 100 per cent oxygen inhalations under 1 to 6 cm water pressure during expiration, immediately following exposure to these gases

Penetrating chest wounds associated with pulmonary edema deserve special consideration In such cases, the necessary active measures were outlined by Brewer and his associates

1 Intercostal nerve block and abolishment of painful stimuli
2 Catheter aspiration of the broncial tree
3 If catheter aspiration is ineffective, bronchoscopy
4 Oxygen inhalation under positive pressure Detailed discussion of this subject is presented in the chapter on Acute Thoracic Injuries

In patients with heart failure, immediate attention to the correction of cardiac insufficiency is imperative while the patient is receiving oxygen inhalations Digitalis alkaloids or strophantin is prescribed in adequate doses If circumstances require, one should give drugs which presumably dilate the coronaries or act as respiratory enzymes in relation to the heart muscle Drugs like papaverine and aminophylline belong to these categories and are useful in improving the efficiency of the heart In addition, attempts at increased diuresis are carried out A combination of mercurials and xanthines may be given orally, intramuscularly or intravenously Simultaneous administration of 1 0 Gm of cevitamic acid in divided doses daily enhances the diuretic effect of mercurials through its influence on the colloidal osmotic pressure of the blood plasma

Sweet and Bland observed symptomatic improvement after surgical anastomosis between the azygos vein and the superior segmental branch of the right inferior pulmonary vein in patients with pulmonary congestion and edema resulting from long standing mitral stenosis

When anaphylaxis is the cause of edema, and it develops after the injection of immune globulin or antiserum, one should apply a tourniquet above the site of injection so as to prevent further absorption of the foreign protein into the general circulation Epinephrine is given in adequate doses (see sections on Asthma) Also, it is advisable to give 50 cc of 50 per cent dextrose intravenously

Satisfactory therapeutic response has been secured in cyclical pul-

monary edema associated with menstruation from x ray irradiation of the pituitary gland

In pulmonary edema of central nervous system or of reflex origin attention must be focused on the underlying primary cause, in addition to proper care of the respiratory emergency

A novel departure in the treatment of pulmonary edema due to cardiorenal insufficiency was introduced by Sarnoff and Farr It is based on the premise that by blocking the lower sympathetic chain, the blood can be pooled in the peripheral circulation thus establishing a shift in the circulatory balance of the blood, which may well be designated as bloodless phlebotomy Consequently, there is a decreased venous return to the heart from the periphery of the body This results in a reduction in the output of the right ventricle Simultaneously, there follows a vascular dilation in the kidneys, with consequent marked increase in diuresis Lower sympathetic block can be attained for a period of two to three hours by injection of novocaine or related drugs into the lower thoracic and lumber sympathetic ganglions Still more prolonged benefits are seen from continued caudal anasthesia which may be maintained for as long as ten days

Venesection is rarely used in the treatment of this condition today Some clinicians are of the opinion that the removal of 300 to 600 cubic centimeters of blood from the circulation is useful in some instances particularly in patients with heart failure and in severe penetrating injuries of the chest In any event, it should be done cautiously and entirely disregarded when the patient is in shock

Wassermann reported favorable results from pressure on the carotid bodies in acute pulmonary edema of cardiac origin

Atropine sulfate has no logical place in the treatment of this condition

The use of morphine is condemned by most experienced clinicians in the treatment of pulmonary edema due to trauma, central nervous system lesions and inhalation of noxious fumes or gases It is a dangerous drug in that it suppresses the respiratory center and thus may add to respiratory insufficiency In heart failure associated with pulmonary edema, morphine in small doses, from one eighth to one fourth of a grain, is permissible Through its effect on the brain, it may alleviate fear, restlessness and apprehension and also sedate the heart Even in such instances, morphine should be given only when the patient is receiving sufficient oxygen There is no excuse for prescribing this drug for the alleviation of cough This symptom can be effectively

relieved by proper treatment of the edema As an adjunct, one may give the patient menthol lozenges or a few swallows of milk Even for the relief of pain morphine is not indispensable For this purpose effective use can be made of one of the synthetic analgesics Methadon also known as amidon and under the proprietary name of dolophine (Lilly) is given in 10 mg (1/6 grain) doses subcutaneously Meperidine, demerol hydrochloride (Winthrop) is administered intramuscularly in doses of 75 to 100 mg (1⅛ to 1½ grains) every three or four hours

Intravenous infusion is hazardous in patients with pulmonary edema Such intervention is bound to increase the intravascular hydrostatic pressure and thus aggravate the edema

The experimental studies of Eaton showed that when pulmonary edema was due to severe blood loss following the injection of isotonic solution of sodium chloride the increase in pulmonary moisture was twice as great as that observed after the administration of whole blood or plasma

Luisada reported on the successful use of ethyl alcohol oxygen inhalations in pulmonary edema He and his associates consider this procedure the method of choice for the treatment of pulmonary edema in patients with shock, in central nervous system lesions and in pregnancy Any humidifier producing good vaporization can be used When alcohol vapors are inhaled through a nasal catheter 95 per cent alcohol is administered When alcohol vapor inhalations are given through a mask, from 30 to 40 per cent ethyl alcohol is placed in the humidifier Maximal benefits are observed usually in one hour or less Occasionally it is necessary to continue inhalations for two hours

Reich and his collaborators observed good results from the inhalation of 2 ethylhexanol (octyl alcohol or octanol) an antifoam agent which is widely used in industry This compound, a colorless liquid was given through a BLB mask with compressed oxygen from a tank as a propellant Either two parts of water with one part of 2 ethylhexanol or unmixed (undiluted) 2 ethylhexanol was given with an oxygen flow of nine liters per hour They also noted that better results followed the inhalation of nebulized 2 ethylhexanol in full concentration when given in combination with oxygen under intermittent positive pressure

Sarnoff and Sarnoff proposed the concept of neurohemodynamic pulmonary edema This term refers to pulmonary edema which results

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from a decrease in the caliber of the peripheral vascular bed, including the veins of the greater circulation This diminution is brought about by systemic vasoconstriction In consequence of this vasocontriction, large volumes of blood will be shifted to the pulmonary circuit The train of events which *follows is elevation of the blood pressure in the* pulmonary vascular bed, including the capillaries, with subsequent pulmonary edema On the basis of their experimental studies, Sarnoff and Sarnoff advocate the treatment of acute pulmonary edema due to hypertension by gradual, moderate dilation of the peripheral vascular bed through lowering the blood pressure of the hypertensive patient They attribute the therapeutic benefits of spinal anesthesia given to patients in acute pulmonary edema to the same mechanism

Pierach and Stotz first treated pulmonary edema with blockage of the RIGHT stellate ganglion with procaine hydrochloride It is assumed that this intervention causes a shift of the autonomic innervation of the lung toward the vagotonic side This is followed by decrease in the permeability of the alveolar epithelium and in a reduction in the blood pressure in the pulmonary artery

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SCLEROSIS OF THE PULMONARY ARTERY AND ARTERIOLES

By ANDREW L BANYAI M D AND J WINTHROP PEABODY M D

Pulmonary arteriosclerosis through popular misconception is regarded as a rare condition Postmortem examinations tend to belie any such concept, for Brenner was able to demonstrate sclerotic changes in the pulmonary vessels in 97 per cent of a series of 100 necropsies Steinberg noted sclerosis in 65 per cent of an unselected series of 500 cases although many cases it is true, represented the disease at a subclinical level

Of instances of clinically significant pulmonary sclerosis most occur in association with various other diseases which are for the most part accompanied by pulmonary hypertension to which the sclerosis is felt to be secondary These diseases include

(1) Congenital or acquired heart disease
(2) Pulmonary diseases
(3) Marked kyphoscoliosis
(4) Infectious diseases
(5) Lymphangitic carcinomatosis of the lungs
(6) Senility

Opposed to the above etiologic types stands primary idiopathic sclerosis of the pulmonary vessels for which no satisfactory etiology can be demonstrated

(1) Congenital or acquired heart disease may lead to the development of pulmonary arteriosclerosis due to the associated pulmonary hypertension (Moschowitz) In mitral stenosis the narrowed mitral ostium leads inevitably to compensatory hypertension in the lesser circulation with resultant arteriosclerosis the degree of sclerosis being proportionate to the amount of mitral occlusion The incidence of pulmonary arterio clerosis in association with mitral stenosis varies from 27 per cent (Posselt) to 98 per cent (Ljungdahl) Mitral insufficiency leads to a similar though less marked degree of hypertension in the pulmonary circuit, which is nevertheless sufficient to favor arteriosclerotic changes A substantial increase in pulmonary arterial pressure likewise occurs in congenital abnormalities, such as septal defects and patent ductus arteriosus where the force of the systemic pressure is transmitted directly to the lesser circulation

(2) Pulmonary diseases likely to cause pulmonary sclerosis are

emphysema, pulmonary fibrosis, bronchial asthma, bronchiectasis, *chronic bronchitis and extensive pleural adhesions.*

Emphysema was originally regarded by Fischer as leading invariably to some degree of sclerosis. On the other hand, Posselt, Ljungdahl, Costa, Yater and Constam have expressed the opinion that the incidence of sclerosis of the pulmonary vessels is no higher in persons with emphysema than in a corresponding age group of nonemphysematous individuals. Between these two extremes stand the observations of Steinberg showing sclerosis in 86 per cent of emphysematous individuals, but in only 62 per cent of a control series. Elevated pulmonary intravascular pressure is regarded as the provocative factor. In the advanced stages of emphysema, the elastic fibres of the lung are largely disrupted. The elastic dilatation of the pulmonary vessels formerly occurring with each inspiration is lost and the pulmonary vascular tree narrowed. This increased resistance results in pulmonary hypertension. In addition, alveoli may rupture and lead to actual compression of the pulmonary vessel, while the enlarged alveoli may compress the vasa vasorum with consequent degenerative changes in the vessel walls.

Pulmonary fibrosis of a diffuse type is capable of producing sclerotic changes either by direct compression of the arteries and arterioles or by secondary anoxemia of the vessel walls by partial occlusion of the vasa vasorum. Any of the chronic lung diseases may develop pulmonary sclerosis via this fibrotic mechanism.

Chronic bronchitis of many years' duration may lead to the development of pulmonary arteriosclerosis. This may be brought about either by the accompanying fibrosis, with its obliterative effect on the blood vessels or their vasa vasorum, or by the markedly elevated intrapulmonary pressure which results from violent coughing. It should be borne in mind that during the compressive phase of a cough, the intrapulmonary pressure may become as high as 160 mm. of mercury, a pressure eight times as great as the normal pressure in the pulmonary artery (20 mm. Hg). Excessive coughing with protracted pulmonary hypertensive levels of this degree can readily initiate atherosclerotic changes.

Bronchial asthma is recognized as another etiologic factor in pulmonary sclerosis. It affects the blood vessels either through the obliteration of smaller segments of the bronchial tract or through the associated fibrosis or emphysema. The two latter factors have been discussed. As regards the former, partial or complete obliteration of the

bronchi takes place as the result of bronchial spasm edema, thickening of the bronchial wall, and accumulation of tenacious mucus in the bronchial lumen. Bronchial occlusion which is widepsread during an asthmatic attack causes a decreased distensibility of the lung. Furthermore, the resulting pulmonary subventilation and patchy atelectasis imply a reduction in lung volume. As a consequence, the pulmonary blood channels become narrowed and thereby offer increased resistance to arterial blood flow, followed by pulmonary hypertension and sclerotic changes. In addition, pulmonary hypertension is augmented by another seldom appreciated factor, viz. the increased negativity of the intrapleural pressure during asthmatic episodes. Increased negativity of the intrapleural pressure develops as the result of a functional dissociation between the lung and the chest wall. This dissocation manifests itself in the lack of inspiratory expansion of the lung due to bronchial obstruction and at the same time in an increased inspiratory effort on the part of the thoracic muscles. When as a result the thoracic cage does expand, the intrapleural pressure becomes more negative. The increased negativity exerts an enhanced suction effect upon the superior and inferior venae cavae with a consequent increase in blood flow into the right auricle, and from there into the lesser circulation leading ultimately to pulmonary hypertension and atherosclerosis. In addition, the histamine liberated during an asthmatic attack has been shown to lead to pulmonary hypertension and must be regarded as a possible contributory factor in pulmonary sclerosis secondary to bronchial asthma.

By depriving the lung of its smooth gliding respiratory motion, obliterative adhesions between the parietal and visceral pleurae may produce a diminished vascular bed comparable to that seen with extensive fibrosis simply by impeding respiratory expansion. Since fibrosis frequently accompanies pleural adhesions of this degree, it is true that a cumulative effect may be considered in such instances of pulmonary atherosclerosis. Similarly, a marked kyphoscoliosis is apt to impede the free flow of blood in the pulmonary circulation with the usual chain of events following the increased resistance.

Infectious diseases which have been considered as possible sources of pulmonary atherosclerosis include influenza, rheumatic fever and syphilis. Cases have been reported in which sclerotic changes were seen on postmortem examination in the neighborhood of chronic pul

monary abscess and fibrocaseous tuberculosis The exact mechanism in such cases is open to considerable speculation

Lymphangitis carcinomatosa has long been postulated as a source of pulmonary sclerosis (Schmidt, 1903) The primary lesion is most frequently gastric and metastasizes to the lymphatics of the lung which characteristically become greatly distended leading to compression and thrombotic changes in the parenchyma Sclerosis ensues and is perhaps hastened by the various toxic factors liberated from the malignant tissue

Arteriosclerotic changes induced by senescence occur less frequently, are of lesser extent and appear at an older age in the pulmonary circulation than in the systemic circulation

Primary sclerosis of the pulmonary arteries and arterioles is a very rare condition As the term implies, characteristic pathologic changes develop in the absence of any demonstrable cardio respiratory disease Involvement of the arterioles is the most typical manifestation of this condition, and it should not be confused with atheromatous changes in the large pulmonary vessels seen in association with systemic arterio sclerosis Although several etiologic possibilities have been proposed, the pathogenesis of this condition remains unsolved

Symptomatology

Since the primary aim of medical practice is early diagnosis, it is well to emphasize that the diagnosis of imminent, or even prospective *right ventricular strain prior to failure is of paramount importance* Thus with congenital or acquired heart disease it is necessary to stress the value of history, physical examination x ray, electrocardiography, and occasionally angiocardiography and venous catheterization in establishing the proper diagnosis Of the acquired cardiac conditions, mitral stenosis is by far the most common cause of pulmonary sclerosis *and the accompanying signs and symptoms should be readily recognized*

The symptoms of emphysema, pulmonary fibrosis, bronchial asthma, bronchiectasis and chronic bronchitis are all discussed elsewhere Extensive pleural adhesions may result from a variety of pathological conditions, and should be kept in mind when the appropriate history is obtained What is most significant to realize is that the transition of these diseases to pulmonary arteriosclerosis is a gradual process marked by progressive dyspnea and cyanosis Whenever dyspnea and cyanosis

develop in a patient who had previously appeared to be well adjusted to his pulmonary disease, the possibility of pulmonary sclerosis needs to be thoroughly investigated

Initially dyspnea occurs only on exertion, later on mild exercise and eventually at rest Anoxemia constitutes the plausible explanation, the basic condition being a diminished carbon dioxide oxygen exchange in the lung due either to obliteration of alveoli (fibrosis) or ineffective tidal air exchange (emphysema) In the event of concomitant left ventricular failure, pulmonary edema may constitute still a third contributory cause

Cyanosis is caused by the accumulation of excessive amounts of reduced hemoglobin in the blood It usually involves the nail beds and mucous membranes, the lips being particularly prominent in this regard but it may progress to an intense degree involving the entire body According to the view of Castex and Capdehourat, cyanosis can best be explained by a dilatation and atonicity of the peripheral capillaries presumably induced by an accumulation of carbon dioxide (hypercapnia) *This peripheral stasis leads to increased oxygen utilization in* the tissues with cyanosis from the consequent increase in the amount of reduced hemoglobin in the blood The superimposed peripheral stasis accompanying the venous congestion of right heart failure may accentuate the picture

Cough is, of course, a frequent complaint in any disease involving the lung Clubbing of the digits (hypertrophic pulmonary osteoarthropathy) is likewise a classical symptom of chronic, protracted pulmonary disease Each, it should be remembered, may occur also in heart disease, clubbing more often with congenital lesions hemoptysis with mitral stenosis, both of which can of themselves initiate pulmonary sclerosis A compensatory polycythemia may be present due to a persistent deficiency of oxygen-carbon dioxide (O_2 CO_2) exchange In the face of pulmonary hypertension the pulmonic second heart sound may be loud and snapping As the right ventricle fails, the second pulmonic sound may become steadily softer

Once right heart failure ensues, the resultant venous engorgement leads to distended peripheral veins, dependent edema and hepatomegaly Ascites and hydrothorax may occur Cyanosis is aggravated for the blood is in longer contact with the peripheral tissues and proportionately greater amounts of reduced hemoglobin pass into the blood

Dyspnea may be somewhat alleviated if pulmonary edema was a significant contributory factor prior to right failure

Diagnosis

In a systematic approach to diagnosis, proper attention should be accorded the past history, symptomatology, physical examination and results of x ray, electrocardiographic and laboratory studies Because of present day limitations the clinical diagnosis of pulmonary arteriolar sclerosis is always indirect and is based on the demonstration of pulmonary hypertension The latter diagnosis is readily apparent when, as a consequence, right ventricle failure sets in One should consider primary pulmonary arteriosclerosis in any case where there is no adequate explanation for right ventricular failure By anticipating pulmonary hypertension, however, one may actually diagnose the condition prior to cardiac decompensation

Physical examination reveals findings characteristic of congenital or acquired heart disease, or those incidental to emphysema, asthma, chronic bronchitis, bronchiectasis, silicosis and other forms of extensive pulmonary fibrosis In congenital heart disease, the murmur is usually systolic in occurrence, although it may be continuous through systole and diastole The murmur may be loud, rough, rumbling, humming or musical and its maximum intensity may be localized in the first, second, third or fourth interspace at the left sternal border Soft systolic murmurs over the pulmonic area are common in young individuals and have no pathologic significance A precordial thrill may or may not be present While it is present at one examination, it may subsequently disappear Findings typical of acquired valvular heart disease need no detailed discussion

The triad described by Ulrich is useful in the diagnosis of pulmonary sclerosis associated with pulmonary hypertension The diagnostic triad consists of

(1) Palpable intercostal pulsations

(2) Pulmonary bruit heard over the entire chest

(3) Fluoroscopically observable rhythmic downward movement of the diaphragm, which is synchronous with cardiac systole and independent of the respiratory excursions

The palpable pulsation is best felt in the second interspace to the left and right of the sternum, laterally in the interspaces in the mid axillary lines, and posteriorly in the lower interspaces The pulmonary

bruit is attributable to stenosis of the smaller branches of the pulmonary artery. Although it is audible over the entire chest, it is more readily detectable in the second interspace and over the right hemithorax. Downward movement of the diaphragm represents the transmission of the pulsation of the pulmonary artery. It is best observed during expiration following deep inspiration and is particularly noticeable on the right side.

Failure of the right ventricle is recognized from distended neck veins, increased venous pressure, dependent edema, hepatomegaly, cyanosis, ascites and hydrothorax. The liver is smooth, and if failure has been acute there may be right upper quadrant pain and tenderness due to tension on the liver capsule. In bedridden individuals, the presacral area is the best site for demonstrating edema. The arm to lung circulation time is prolonged. Occasionally a slight degree of jaundice occurs from protracted hepatic congestion.

The electrocardiogram is of value in demonstrating the presence of right ventricular strain or cor pulmonale, the characteristic pattern being known as right axis deviation. This is marked by inversion of the QRS complex in lead I while it remains upright in lead III. Early changes appear as a gradual lowering of the R wave and deepening of the S wave. In advanced cases, the former descends to the isoelectric line while the S wave occupies a position far below that. In addition to organic changes in the heart or lungs which may cause right axis deviation, the latter is also noted in patients with low diaphragm and a consequent vertical position of the heart, in cases with displacement of the heart by large pleural effusion, pneumothorax, pulmonary contraction, massive atelectasis, pulmonary infarction, congenital dextrocardia, and left ventricular premature beat. Absence of right axis deviation does not rule out right ventricular strain or cor pulmonale.

Electrocardiogram is likewise valuable in acute cor pulmonale in which a sudden complete cardiac breakdown occurs in an individual with long standing pulmonary disease. Here in addition to right axis deviation one finds low amplitude QRS complexes in lead II, isoelectric, diphasic or negative T waves in lead II and negative T wave in lead III.

Roentgenologic examination of the patient is essential for diagnosis. The lung fields are inspected for evidence of disease. The size, shape and motion of the thoracic cage are noted and the position and respiratory excursions of the diaphragm are observed. Cardiac change may

pulmonary edema In patients with peripheral edema it is necessary to rule out nutritional edema liver disease nephrosis, and various similar conditions

Prognosis

The prognosis must be predicated upon the underlying disease When this condition is too far advanced or its progress cannot be halted (e g, third stage silicosis), then the prospect of altering the fatal course is unlikely In other instances, when the patient s cardiac condition is still amenable to treatment every attempt should be made to alleviate the right ventricular strain by prompt attention to the causative pulmonary disease Measures directed toward the adequate treatment of asthma emphysema, chronic bronchitis, bronchiectasis and other underlying conditions should be instituted without delay If intervention of this type is instituted early and competently, then additional strain is obviated the patient s complaints may be substantially relieved *progress of the right ventricular hypertrophy halted* and one can secure for the patient a reasonably long life expectancy in acceptable physical comfort

In instances when the patient is seen with extensive, irreversible lung changes which induced the development of cor pulmonale, the disease follows a downhill course The latter may be brief or more prolonged, depending upon cardiac tolerance and reserve Also, it is greatly influenced by intercurrent diseases The prospect is that the *patient will die either of heart failure or intercurrent infection* Failure of the left ventricle, which may result from anoxia, is of grave prognostic significance

Treatment

Therapeutic measures are directed toward the immediate alleviation of disturbing symptoms and are planned on the basis of cardiopulmonary findings and coexistent complications It is mandatory to ascertain the source of dyspnea and to institute treatment accordingly *The most important measures in this regard are* oxygen inhalation and digitalization Dietary salt restriction is a necessary adjunct in preventing or relieving edema

Significant improvement in the patient s condition may be achieved *by regulating his daily regimen Assuming that the patient is not* bed ridden, his physical activities must be reduced to a minimum No exercise or exertion of a degree sufficient to produce dyspnea *is* per

missible Resting in bed or in a comfortable chair with the feet elevated, is recommended after each meal

While digitalization effects a mobilization of edema fluid by augmenting the cardiac output there are other agents diuretics which supplement and enhance this action by a direct renal effect The mercurial diuretics constitute the most satisfactory diuretics in use today, acting by diminishing tubular reabsorption The mercurials with a theophylline linkage (mercupurin mercuzanthin mercuhydrin salyrgan etc) all enjoy a wide range of utilization Recent reports attest the superiority of another mercurial diuretic thiomerin which has replaced the theophylline component with a mercaptan sodium thioglycollate This drug appears to have a greatly decreased level of toxicity, plus a greater ease of administration Because of its subcutaneous route of administration it is possible that thiomerin like insulin may eventually be injected in maintenance doses by the patient himself without trepidation or decrement in diuretic effect

Close attention to the patient s weight serves as a good index of his cardiac state Salt restriction should be enforced but an adequate dietary intake should be maintained Digitalization and diuresis should be promptly effected when the indications arise In addition pregnancy should be strictly avoided obesity prevented or corrected as the case may be Should mental tension anemia or intercurrent infection occur the treatment need be most vigorous and is best effected by a program aimed at prevention Any underlying contributory condition should be handled by the specific therapy indicated In general a regimen should be outlined wherein the crippled heart and handicapped lung are carefully protected from any strain whatever

Ayerza's Disease

Abel Ayerza, in 1901, described a syndrome in an unpublished lecture at the National University of Buenos Aires, characterized by severe cyanosis which gave the patient an almost black appearance This symptom was associated with dyspnea hypertrophy of the right ventricle and polycythemia On account of the deep and violaceous cyanosis, Ayerza aptly referred to these patients as cardiacos negros or black cardiacs The postmortem examination in the first case so designated revealed the following significant findings peribronchial fibrosis, dilatation of the bronchi, hypertrophy and dilatation of the right ventricle Although Ayerza is being given due credit for the clas-

pulmonary edema In patients with peripheral edema, it is necessary to rule out nutritional edema, liver disease, nephrosis, and various similar conditions

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sical description of this condition, its fundamental pathologic manifestations were recognized by Andral as early as 1829, and a correlation between typical pathologic changes and clinical findings was recorded by Romberg in 1891.

In connection with early case reports by Arrilaga, Escudero and others, it was thought that Ayerza's disease was due to syphilis. Definite divergence of opinions developed as to the pathogenesis of this disease. Arrilaga advanced the idea that syphilitic arteritis was the provocative lesion and it was followed by changes in the bronchi. Escudero, on the other hand, expressed the opinion that syphilitic bronchitis was the initial lesion and subsequently it caused an involvement of the pulmonary blood vessels. The preponderance of opinions indicates that the syndrome of Ayerza may follow a great variety of pleuropulmonary or cardiac diseases. Also, it is generally accepted that its characteristic clinical manifestations are attributable to the same factors which are responsible for the symptom complex associated with advanced pulmonary *hypertension and pulmonary arteriolar sclerosis.*

It is a part of sound medical thinking to accept the so called black cardiac disease as the final stage of a condition which has its beginning, as a great many other chronic diseases, in irrelevant structural and functional alterations. Thanks to the wide margin of reserve and compensatory capacity of the cardiorespiratory system, early involvement of these vital organs may remain subclinical. This asymptomatic phase is followed by a gradually increasing development of symptoms corresponding to the underlying organic changes. A so called catarrhal stage of the disease, which is emphatically mentioned by South American and French clinicians, is seen only in patients who develop Ayerza's disease in consequence of a protracted infection of the lower respiratory passage. Catarrhal onset has also been reported in individuals with primary pulmonary arteriolar sclerosis. In any event, as the underlying cardiovascular or pulmonary changes become more extensive and more inclusive an increase in the patient's symptoms and signs is noted. For these reasons, therefore, it seems preferable to look upon Ayerza's disease, not as an independent clinical entity, but as the result of a progressive disease of heterogenous origin. Basically, it is a grave manifestation of cardiopulmonary insufficiency due to pulmonary hypertension with pulmonary arteriolar sclerosis.

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develops through thrombosis or by granulomatous proliferation Usually, there is a partial or complete necrosis of the diseased vessel wall Development of small, localized aneurysms is common There are some secondary pathologic manifestations, such as stasis, infarction, hemorrhage due to rupture of an artery, fibrosis and edema Purulent bronchitis and bronchopneumonia may accompany the aforementioned changes The inflammatory exudate in the bronchi contains an extremely large number of eosinophilic leucocytes There is a hyaline thickening of the basal membrane of the bronchi, also, eosinophilic infiltration of the bronchial wall may be observed

Periarteritis nodosa occurs during any age period, from childhood to old age but it is more likely to be seen in persons of middle age Its incidence is three times as great in males as in females Although combination of involvement of several organs and structures is a common finding, it is customary to distinguish various forms of this disease on the basis of prominent presenting symptoms and signs Accordingly, one recognizes renal, cardiac, gastro intestinal, neuromuscular, cerebral, cutaneous and pulmonary types

Symptomatology

In about 20 per cent of patients with periarteritis nodosa, asthma is present *Evidently branches of the pulmonary artery represent the main* shock organ of hypersensitiveness in such cases The onset of this condition is insidious or sudden The two types occur with about equal frequency The duration of the disease with chiefly pulmonary involvement varies from a few months to six years Unusually severe forms of asthma are not uncommon Associated respiratory symptoms include cough which is especially marked after exertion and may be productive of mucoid or mucopurulent sputum The latter is occasionally blood-streaked Frank pulmonary hemorrhage has also been observed It results from necrosis and perforation of the vessel wall and may follow pulmonary infarction Sternberg reported a case of fatal pulmonary hemorrhage in periarteritis nodosa Dyspnea on moderate exertion is noted in more than 50 per cent of the cases Sometimes the patient is orthopneic and complains of pain in the chest

In addition, there may be a diverse array of complaints depending upon the extent of simultaneous involvement of other organs These include nausea, vomiting, hematemesis, intestinal hemorrhage with bloody stools, abdominal pain, jaundice, paresthesias (numbness,

tingling) in the extremities, swelling of the ankles and wrists, arthritis, increasing muscular pain, tenderness and stiffness, palpitation, headache, visual disturbances, vertigo, convulsions, coma and nocturia General symptoms which are likely to be encountered are fever, fatigue, malaise, profuse sweating and marked loss of weight

Diagnosis

The patient may present himself with the history of chronic bronchitis or asthma The clinical manifestations of asthma due to peri arteritis nodosa are the same as those of genuine bronchial asthma On physical examination, one may note that the patient is undernourished or emaciated The latter condition is seen in about 50 per cent of the cases Meyer (1878) who first described the clinical findings in this disease referred to the association of emaciation and anemia in these patients as chlorotic marasmus To this he added polymyositis, poly neuritis and gastro intestinal disturbances On inspection one may find cyanosis and labored breathing Fever is usually low or moderate, inter mittent or remittent, but it may reach 104° F (40° C) According to Boyd and Nussbaum, tachycardia out of proportion to fever is suggestive of periarteritis nodosa Muscle weakness and tenderness may be detec table On close scrutiny, palpable subcutaneous nodules are found along superficial arteries in about one sixth of the cases The respiratory excursions of the chest are limited The percussion note over the lung is normal or hyperresonant On auscultation harsh breath sounds are heard, together with sonorous sibilant and fine moist rales all over the lungs Pleural involvement is detected from the presence of friction sound or signs of effusion Pleural changes may be unilateral or bilateral

Roentgenograms of the chest reveal enlargement of the hilar struc tures, accentuation of the bronchovascular markings and widely distrib uted small, nodular shadows in both lung fields There may be a pre dominance of the nodular shadows in the lower one half of the lung The hilar and broncho vascular shadows show a decrease when the patient s condition improves only to recur subsequently Pleural effusion is identified from the characteristic homogeneous dense shadow it casts on the x ray film

Roentgenologic appearance of periarteritis nodosa may be similar to that found in conditions enumerated in the differential diagnosis of Pulmonary Manifestations of Lupus Erythematosus

Conclusive evidence of periarteritis nodosa is found in muscle biopsy

(deltoid, gastrocnemius) or in biopsy of subcutaneous nodules However, it is well to point out that laboratory findings are of importance in two ways First, by ruling out other diseases which should be taken into consideration, with the aid of specific complement fixation, precipitin tests and skin tests (tuberculin, brucellergen, Bachman and others) Secondly, the differential count of the white blood cells is of significance While eosinophilia occurs in 36 per cent of patients with periarteritis nodosa, in general, its incidence is over 90 per cent in individuals with asthma caused by periarteritis nodosa Eosinophilia may reach 84 per cent in these cases Because of the rarity of eosinophilia over 15 per cent in uncomplicated bronchial asthma, Wilson and Alexander suggested the likelihood of periarteritis nodosa in patients with bronchial asthma whose eosinophile count is over 15 per cent The total leucocyte count *may remain within normal limits, but in some cases it reaches up to* 30,000 per cubic millimeter The sedimentation rate of the erythrocytes is usually accelerated

Prognosis

There are great variations in the duration of the disease Its course is influenced by the severity and extent of the pulmonary lesion and by the concurrent involvement of other vital organs The prognosis is, in general, unfavorable The treatment is symptomatic and supportive Attempts should be made at removing or counteracting the causative allergen Recent reports of effective treatment in a few cases with ACTH or cortisone warrant further trial Reports have been made of arrest of the progress of the disease by administration of paraaminosalicylic acid

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CHAPTER X

BRONCHIAL ASTHMA

BRONCHIAL ASTHMA IN CHILDREN

By BRET RATNER, M D

Pathogenesis

PRACTICALLY all students concerned with allergy in adults find that from 50 to 60 per cent of their patients give a history of onset in childhood. Cooke and his co-workers adduced from their studies that the greater the degree of inheritance, the earlier will allergic phenomena manifest themselves. These observations, however, were largely concerned with adults. Studies on asthma by Bray, Peshkin, O'Keefe and Ratner, Silberman and Greenburgh, dealing exclusively with children, led us to conclude that the inception of this syndrome is not as strongly influenced by heredity as it is generally believed. That there are more affected children in a small percentage of families with a strong familial allergic tendency cannot be denied. While one may have to admit, therefore, that a greater susceptibility for allergy does exist in certain children, it has not yet been satisfactorily proved that the actual age of onset is influenced to any great extent by genetic factors.

One must be alert to the early beginnings of respiratory allergy. In some instances it is ushered in by recurrent episodes of sneezing, lacrimation, rhinitis and coughing. The early episodes will perforce be treated symptomatically, but if these recur time and again, the possibility of the more serious allergic manifestations, hay fever and asthma, must be considered. Eczema, on the other hand, may in many instances be a forerunner of asthma. This is generally accepted by investigators in this field, and should become common knowledge to all physicians.

Orientation with respect to the basic mechanism underlying allergy is essential for the proper management of the patient. There is little that can be found in the literature to contradict the antigen-antibody hypothe

sis, namely, that hypersensitive reactions in various tissues result from an interaction of circulating foreign antigen with its specific antibody, the antibodies having become fixed to tissue cells at some time prior to the reaction

Whether histamine, which is released, is the direct cause or the result of the reaction, is still problematic Yet the proponents of the histamine theory only tacitly accept the antigen antibody mechanism and would have us believe that this chemical is of major importance in the production of the allergic reaction All therapeutic efforts with this viewpoint in mind are directed towards the neutralization of histamine Unfortunately, the antihistaminic drugs, recommended for this purpose, at best afford only symptomatic relief Epinephrine, ephedrine and atropine still remain reliable drugs for the relief of allergic symptoms because they do relax the spasms which result from antigen antibody interaction and the good effects of the antihistaminics appear to be due to the same action

When the distribution of allergic syndromes are viewed as a whole, asthma is found to be the prevailing allergic syndrome Whenever there is a multiplicity of syndromes, asthma is generally one of the complicating conditions

The fact that asthma seems to be the dominant manifestation of allergy makes it apparent that the lung structure is conspicuously predisposed to sensitization This must in large measure be due to the great amount of smooth muscle present in the terminal bronchioles, and it is here that the reaction ensues when the specific antigen gains entrance into the body The histamine theory does not explain this predilection for lung tissue as well as does the antigen antibody hypothesis

Pathology

Acute anaphylactic death in the guinea pig due to complete bronchiolar constriction was early correlated with human asthma by Meltzer However, though acute anaphylactic death in the guinea pig can be compared with anaphylactic death in the human, the chronicity of asthma produces a distinctive pathology Briefly stated the pathologic picture in patients dying from asthma comprises the following

(1) Emphysema, lobular or universal
(2) Edema of the bronchial wall
(3) Sacculation of the epithelial layer of the bronchi

(4) Hypertrophy of the bronchial musculature

(5) Thickening and hyalinization of the basement membrane of the medium sized bronchi and occasionally of the bronchioles and large bronchi

(6) Increase of mucus in the bronchial and glandular lumens and mucous plugs in the large and medium sized bronchi

(7) Hyperplasia and hypersecretory activity of the goblet cells of the bronchi and mucous glands

(8) Degenerative changes of the cartilage cells of the bronchi

(9) Eosinophilic infiltration of the bronchial wall, peribronchial tissues subepithelial layers and at times the bronchial lymph nodes and alveoli

(10) Bronchial and bronchiolar stenosis caused by the exudative and bronchomuscular systems

Differential Diagnosis

It may be edifying to cite several cases in which the intricate pattern of a differential diagnosis is demonstrated

PERTUSSIS

An infant of three months was referred to me because of a severe intractable cough, present throughout the day and night, which had persisted for two weeks The baby was losing weight and in general was not thriving The physician who referred the case had come to the conclusion that it was an allergic cough because, on occasion, he had heard sibilant rales I did not immediately resort to tests because of the age of the child We did a blood study which revealed a white count of 18,000 with a *79 per cent lymphocyte differential* Despite the absence of a whoop, I made a tentative diagnosis of pertussis We obtained human convalescent pertussis serum from The Philadelphia Serum Exchange and administered three successive doses of 20 cc intramuscularly at 48 hour intervals The prompt subsidence of the cough was the most dramatic I have ever witnessed

CYSTIC FIBROSIS OF THE PANCREAS

Another infant of eight months of age, who was marasmic and suffering from a persistent cough since the first few weeks of life, was sent to me as an allergic subject Before coming, he had been skin tested by a laboratory and was said to have been sensitive to a motley group of antigens These proved subsequently to have nothing to do with the case *Here too sibilant rales had been heard* by the attending physician The

nature of the stools, the high polymorphonuclear count, the marked marasmus and the finding of a patch of pneumonitis led me to make a tentative diagnosis of chronic cystic pancreatitis This diagnosis was finally corroborated by laboratory examinations Pertinent data are given in the respective section

TUBERCULOUS TRACHEO-BRONCHIAL NODES

Another cause of intractable cough in infants may be the pressure of tuberculous lymph nodes on the tracheo bronchial tree, causing a passive bronchoconstriction in which the physical signs may simulate those of asthma

NONSPECIFIC FACTORS

Non allergic episodes in the asthmatic child must also be considered Those of less serious import are the coughs following strenuous exercise, or those which result from irritation produced by strong odors, such as fresh paint, camphor, etc Each situation must be carefully evaluated and differentiated from truly allergic episodes

Psychosomatic incidents occur only too frequently once the cough pattern is established, and should be borne in mind

Attention must also be called to certain pulmonary complications which may occur in asthma of long duration Amongst them is emphysema, which fortunately is rare today, probably because so few children have rickets that may have been responsible for the widening of the thoracic wall

LOEFFLER'S SYNDROME ALLERGIC PNEUMONITIS

Conditions that have engaged our attention recently are various types of "allergic pneumonitis " Detailed discussion of this subject is presented in the respective section

Status Asthmaticus

It might be helpful at this point to discuss the etiology of the prolonged state of asthmatic dyspnea, i e, status asthmaticus, from the viewpoint of the pediatrician rather than that of the trained allergist To my mind, the type that is met with in adults does not often occur in childhood When one does see it, particularly in the young infant it requires all the ingenuity of the attending physician to cope with the terrific struggle against death If every case of uncontrollable dyspnea is diagnosed a priori as status asthmaticus, difficulties will be encountered This state may be due to many and varied causes and therapy depends upon the underlying pathology

An active bronchiolar constriction which is the basic physiologic

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pathology in true allergic asthma, with a secondary edema of the mucosa and possible plugging of the bronchi are the conditions most frequently found in status asthmaticus of adults In childhood, the overwhelming majority of cases of prolonged dyspnea resembling status asthmaticus cannot be explained on the allergic basis

Hanzlik and Karsner attribute the mechanism of anaphylactoid phenomena *in guinea pigs to "passive bronchoconstriction," i e, a nar* rowing of the bronchial tube due to outside pressure (thrombosed pul monary vessels in their instance) This differs from active broncho constriction which results from a spasm of the bronchiolar smooth muscles

The term "para asthma devised by Peshkin is useful and should be generally adopted to describe the conditions resulting from passive bronchoconstriction He classifies this type among the non protein sensi tive forms which clinically cannot be distinguished from other types of asthma It is usually caused by an enlarged thymus or enlarged bronchial lymph nodes, or both

"Obstructive asthma might in large measure be applied to all condi tions resulting in status asthmaticus, for even the true allergic bronchiolar constriction has as a complicating factor mucous plugs in the bronchi

It might not be amiss to refresh our minds as to the causes that may be *responsible for status asthmaticus in the young infant*

(1) A foreign body in the esophagus may compress the trachea by its bulk or by the secondary swelling or by both

(2) Thymic compression stenosis

(3) Substernal goiter, sometimes congenital

(4) Adenopathy—the most common site is at the bifurcation of the trachea

(5) Cicatricial stenosis due to (a) a suppurating mediastinal gland, or (b) to a prolonged sojourn of a foreign body

(6) Endobronchial foreign bodies

(7) Subglottic laryngitis associated with subglottic edema

(8) Papillomas of the trachea or larynx

(9) Pulmonary abscess, bronchiectasis or laryngotracheobronchitis

(10) Acute massive atelectasis or collapse of the lung

(11) Anaphylactic shock (non fatal) resulting from injection

(12) Massive contact with an allergenic dust

(13) Double aortic circle or other vascular anomalies

In view of these many causes of prolonged and severe dyspnea in

childhood it is helpful to bear in mind the aphorism All is not asthma that wheezes

I recently saw two new borns who appeared to have status asthmaticus We discovered that the symptoms of one were due to a papilloma of the trachea and of the other to material inspired during delivery Had the conditions not been properly diagnosed and appropriate treatment instituted the outcome in both instances might have been fatal Curiously both infants were moderately relieved by adrenalin but oxygen had to be resorted to and the obstruction removed before the prolonged asthmatic breathing cleared I can assure you that we spent many anxious hours with these cases of so called asthma in the new born

A frequent cause of status asthmaticus in the young infant is illustrated in the following case

A child one year of age was admitted to the hospital suffering from severe and unremitting dyspnea Sibilant and sonorous rales were the dominant lung signs Adrenalin had no effect on the severe asthmatic breathing Although there was no history of tuberculosis a Mantoux test was strongly positive The x ray picture revealed an enlargement of the tracheobronchial glands and massive consolidation of the hilar region A tuberculous gland was also noted in the inguinal region The infant died after 18 days of unremitting asthma Necropsy corroborated the clinical diagnosis

I have also observed an instance of recovery from tuberculous involvement simulating asthma and Peshkin and Fineman have reported similar cases Lapage and Adams cite the case of a young child with uncontrollable asthma who suddenly coughed up large pieces of debris from a calcareous gland as have others

I should like to cite two cases of status asthmaticus accidentally induced by intracutaneous test injections A nine year old boy hypersensitive to milk received 0 02 cc. of 1 per cent pure lactalbumin intracutaneously He promptly developed severe dyspnea which persisted for four days Repeated small doses of adrenalin oxygen therapy and phenobarbital finally relieved him The second case was that of a horse dander sensitive child who developed status asthmaticus which lasted for five days after an intracutaneous test with horse serum He was treated by the same procedure as the former case and finally recovered

I have perhaps dwelt too lengthily upon the suggestions for diagnosis but since therapy depends so largely upon diagnosis it seems to me that

syndrome should arouse one s suspicions, especially if preceded or accom panied by eczema, urticaria, or recurrent attacks of so called colds or vasomotor rhinitis During the period of observation, much valuable data can be obtained by careful questioning relative to diet and environmental factors One can intimate to the parents that allergy is suspected as the cause for the child s illness Thus prepared with the information that recurrent episodes are to be expected, they will cooperate more fully with the physician in analyzing the circumstances surrounding the attacks

VALUE OF FLUOROSCOPY AND RADIOGRAPHY

Each asthmatic episode must be evaluated by the physician in charge A striking example is the case of a child who lived at a great distance The frequency of attacks in this three year old child gave the physician in charge a false sense of security The mother called him and, after listen ing to the complaints, he told her that little Jeffrey probably had another one of his attacks and proceeded over the phone to prescribe symptomatic treatment Several days later, the child died of an overwhelming lobar pneumonia diagnosed the day before death by x-ray, sputum and blood examination I have had several cases with asthmatic symptoms that, by fluoroscopy and film, proved to be true intercurrent pneumonia which cleared up with penicillin and sulfa therapy Contrariwise, a high tem perature should not lead to a diagnosis of pneumonia in an asthmatic child, temperature elevations do occur in uncomplicated asthmatic attacks—contrary to general belief—especially in young children The use of the fluoroscope is as essential as the stethoscope in ruling out lung pathology and, at times, the only reliable means of doing so Recently, also, two patients came in supposedly suffering from an attack of asthma which, in both instances, proved to be the first stages of measles

PROTEIN SKIN TESTING

I stress delaying the diagnosis of asthma and resorting to skin testing because much harm is done by too hasty an employment of this proce dure Many cases of allergy tested in the early stages will give completely negative results It requires time for the skin to become sensitized In some instances, the condition is evanescent and clears up spontaneously Hence, the physician would do well to refrain from referring a case for testing until the child has had several attacks over a period of at least a year Once having embarked on skin tests, they should be done with thoroughness It must be realized that despite its limitations, the protein skin test

are not available, the old ones must be carefully covered Wood and metal chairs are preferable to the overstuffed variety

Immunization against environmental substances is not always effective and, for the most part, I do not advise it It is far better to reduce dust contact in the house, in the manner outlined, and to permit a moderate amount of contact outside the home The child will thus gradually build up an immunity in a natural manner

FOOD

For alleviation of symptoms due to suspected food sensitivities much can be accomplished by the employment of a heat denatured diet composed of freshly heated evaporated milk, or raw milk boiled for at least one-half hour, thoroughly boiled meats of all varieties, broths and soups of all varieties, hard boiled eggs, pre-cooked cereals (such as Pablum and Pabena) and cereals cooked for prolonged periods, spaghetti and macaroni, dextri-maltose, corn or cane sugar, thin melba toast and Ry-Krisp, thoroughly cooked vegetables, stewed fruit, jams and jellies The emphasis is upon long and thorough cooking in the presence of moisture Since this diet is devoid of any fresh fruits and vegetables, vitamin C must obviously be provided by adding 50 to 100 mg ascorbic acid a day

The environmental control should be permanent With the foods, however, after all symptoms have disappeared for a prolonged period, and the child is thriving, one fresh food, or lightly cooked food, at a time may be added to the denatured diet and, if well tolerated, may be continued Thus it may be determined empirically what foods are at fault, and these incriminating foods must be continued in the heat-denatured form when the patient returns to an otherwise normal diet This empiric approach may be successful in many simple cases

A bronchoscopist recently scoffed at allergists because he claimed he *never was aided by their "innumerable tests"* This *may have been true* enough, for the asthmatic breathing in his case may undoubtedly have been due to obstructive bronchial or parenchymal lung pathology *In* young children, therefore, be sure you are dealing with true asthma before proceeding with treatment

Certain Phases of Diagnosis and Treatment

It is a mistake to make a definite diagnosis of asthma on the basis of an isolated attack of dyspnea, even if accompanied by the objective finding of sibilant and *sonorous rales* Only repeated occurrences of such a

rule have multiple sensitivities and the process is far more intricate In my experience, really salutary permanent results in such cases can be achieved after one to several years of observation and therapy, though often benefits may be perceived early in the course of treatment Remissions are too often encountered and unless the parents are carefully educated so that they may take cognizance of all complicating factors, results may be discouraging

Specific allergenic treatment may be resolved into three phases 1) elimination, 2) substitution, 3) immunization

VALUE OF VACCINE THERAPY

For the enhancement of the general immunity response of the patient, it is of inestimable value to inject small doses of stock vaccines, including a large variety of bacteria These injections can be given at weekly or fortnightly intervals Here, too, the caution with respect to large reactions must be observed If the reactions are large, the dosage must be considerably reduced by diluting the vaccine one tenth, one hundredth or one thousandth fold The anamnestic reaction then gathers full momentum and the child, after a period of such treatment, develops immunity in the same way that he develops a natural immunity to diphtheria and other contagious diseases through minimal subclinical contacts The nonspecific effect of the anamnestic reaction in some unknown manner stimulates antibody formation in general Autogenous vaccines have no particular advantage over the stock vaccines

Symptomatic Treatment of the Asthmatic Attack

This particular phase of the problem is of the greatest interest to us as physicians Above all, a cheerful attitude should be maintained by those surrounding the patient If the child is breathing forcefully, and is not cyanosed, there is little danger The harder he breathes, the better If a child is cyanosed and has very shallow breathing or apnea, the situation is serious If the sounds on auscultation are clear, loud and resonant, with sibilant and sonorous rales, the asthmatic attack is of no serious consequence If auscultation discloses feeble sounds and there are moist rales, it is indicative of bronchial plugging Temperature elevation may occur in the asthma of childhood, as has been stated, do not be misled and change the diagnosis to pneumonia

It is my belief that asthma due to bronchiolar constriction is usually promptly relieved by adrenalin or ephedrine Asthma due to bronchial plugging, on the other hand, is not relieved by antispasmodics, but only

does compare favorably with other important diagnostic procedures—very few of which are infallible—and should not be scoffed at

Perhaps the best method to be employed in children is the scratch test, because it is painless and as many as 35 to 50 tests can be performed on the back at one visit Anaphylactic shock has never been known to develop from a scratch test This cannot be said with the same degree of assurance for the intradermal test The scratch test when performed and interpreted intelligently is far more delicate and fewer false reactions are obtained The intradermal test, however, may prove useful in instances in which the scratch tests are entirely negative or only suggestive in character

It has long been thought that food sensitivities play the dominant role in allergy of childhood That does not prove to be so, for throughout infancy and childhood sensitivities to foods, inhalants and contactants run a more or less parallel course Multiple sensitivities are the rule and not the exception Therapeutic measures may fail completely if all possible offending factors are not taken into account For this reason, if the child is subjected to study he should be tested with all available proteins More and more tests, rather than fewer and fewer, should be our aim Unfortunately the tendency is to do fewer tests

Tests with extracts made from the dust producing articles indigenous to the child s direct environment are very important and helpful Investigations have shown that changes occur as certain materials age for example, stuffings in mattresses, pillows, etc , molds develop and other substances are found which produce antigenic properties not present in the new material Skin testing is not the sole diagnostic procedure essential for the proper appraisal of all the factors involved in this complicated problem The child must be studied and treated as a whole The family history, the specific history of the child and an investigation of the environment, all aid in the appraisal of the case A complete chemical examination of the blood, blood and nasal cytologic studies, roentgenograms of the sinuses, chest and wrist bones, Mantoux test, urinalysis, and psychosomatic factors help to appraise and rule out secondary factors

Value of the Skin Test

Having discovered the specific offenders, brilliant results may, on occasion, be achieved merely by the elimination of the incriminating proteins This may simply necessitate the removal of an animal pet, or a particular piece of furniture However, intractable cases of asthma as a

An additional fact to be borne in mind is that an oleoma may result n an injection of this combination Once the oil tumor is formed, ay have to be excised because it has a tendency to continue to destroy ue and grow larger

RENALIN (1 100) INHALATION

If the premise, that the action of adrenalin is immediate, is correct, en one or two series of inhalations should be sufficient for relief of an ttack of asthma. In my experience, when a patient is given an inhalation utfit, he tends to use it excessively I have therefore come to regard this procedure as a dangerous one and forbid its use for the following reasons

(1) Epinephrine is a habit forming drug Administration by inhalation is probably the most habit forming type of therapy because the simplicity of use tempts the patient to reach for it at the slightest provocation I do not use the term "habit forming" in the same sense that we speak of addiction to morphine, but rather to imply that, since a patient does get relief in certain acute seizures, he may become dependent on it and is tempted to administer it to himself for its stimulating effect when it may not be altogether necessary It gives the patient a "lift" I recently had a child of twelve who was so dependent on it that she inhaled adrenalin every night before retiring for fear that she might otherwise suffocate It took four months to rid her of the habit She now states that at times she really misses the exciting stimulus it gave her

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through emesis, steam inhalation and expectorants The bronchiolar constriction usually results from foreign antigens, such as food or serum which enter the blood stream and act directly on the sensitized bronchiolar musculature producing spasm The bronchial plugging is usually due to an inhalant which enters the air passages directly and produces its chief reaction in the lumen of the bronchi, with edema, excess mucous secretion and resulting obstruction

Can a child die during an attack of asthma? May such a death result from faulty treatment? These are questions always posed when asthma is the subject of discussion Because of the anxiety and fear engendered in the parent and child by an attack of asthma, this syndrome appears in the forefront of emergency practice and the symptomatic therapy of the asthmatic attack is therefore of great interest to the physician

Choice of Drugs

I should like to emphasize the fact that amongst the most serious errors I encounter are overmedication and a bad choice of drugs

ADRENALIN (EPINEPHRINE)

If the aim is to produce relief of bronchiolar spasm, small amounts of adrenalin will produce the desired effect A child should never be given an injection of more than 2 or 3 minims It should be injected subcutaneously or intradermally and never intravenously or intramuscularly There is no objection to the repetition of the same small dose at intervals of 20 or 30 minutes Large doses only tend to cause a further bronchiolar constriction Further deleterious effects of large doses (0 5 to 1 0 cc) are (a) the enhancement of apprehension, (b) acceleration of pulse, (c) rise in blood pressure, (d) pounding headache, (e) cardiac syncope, and (f) pallor The result to the patient psychologically is the superimposition of a greater feeling of disaster than he is already experiencing from the asthma, and physiologically an increase in pulmonary vascular congestion

ADRENALIN IN OIL

Adrenalin in oil has been advocated to allay the bad effects of large doses and for prolonged action I see no need for such a therapeutic agent in children

Adrenalin is not a drug that can be used for a long range effect It either works promptly or not at all It is only effective in the alkaline medium of the blood but a short time, for it retains its potency only in an acid pH

An additional fact to be borne in mind is that an oleoma may result from an injection of this combination Once the oil tumor is formed, it may have to be excised because it has a tendency to continue to destroy tissue and grow larger

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(2) Since there is no control of dosage, an unusually large amount may be absorbed, and the consequences may be grave

EPHEDRINE

What has been said relative to the action and overdosage of epinephrine holds for ephedrine as well, though to a lesser degree Thoughtless and excessive use of ephedrine in nose drops may result in the absorption of large *amounts Ephedrine sulphate therefore should be prescribed for* a given attack and only several doses be advised

Type of Asthma in Relation to Therapy

In 1939 I published a study on experimental asthma in the guinea pig As a result of these studies I have come to the conclusion that asthmatics may be divided, broadly speaking, into two groups 1) those suffering from asthma due to a bronchiolar spasm, and 2) those suffering from asthma due to a bronchial obstruction The classification is not rigid, and one individual may present both types The bearing that

this classification has on drug therapy of severe asthmatic attacks, and particularly status asthmaticus, is the point of emphasis

In the bronchiolar spasm type, the antigen reaches the bronchioles via the blood stream and adrenalin will work like a charm We find this type in food sensitive cases, and it is the one often encountered in early childhood The same form occurs in serum sensitive patients following an injection of a specific serum, and it is relieved by adrenalin if the shock is not too profound

Let us now turn to the child who is given injection after injection of adrenalin without the slightest relief Why doesn't adrenalin help? What about the child who has been in a state of status asthmaticus for several days? The answer as I see it is that in such cases it is not the bronchiolar spasm that is predominant, but an edematous state of the lumina of the bronchi with marked bronchial plugging This we learned from our guinea pig experiments When the animals inhaled antigenic dusts, the allergen coming into direct contact with the lining and vessels of the larger air passages, produced edema and increased secretion which resulted in obstructive symptoms On the other hand, in anaphylaxis after intravenous injection, the allergen coming in contact with the smooth muscle of the terminal bronchioles, produces bronchiolar spasm The object lesson is evident

The Use of Syrup of Ipecac in Refractory or Obstructive Asthma

If a bronchiolar spasm is the cause of the symptoms, the administration of adrenalin will bring about relief If no relief ensues from repeated injections of adrenalin, then we must be dealing with an obstructive bronchial asthma due in all probability to some inhalant allergen which has entered the air passage directly Cease adrenalin administration and order some syrup of ipecac!

For infants and young children give one half to one teaspoonful, if this does not induce emesis, give two teaspoonfuls For older children and young adults, repeated doses may be given until the desired result is produced Follow the ipecac with lukewarm water to further its effectiveness If this therapy is effective, the result is brilliant, because relief from distress follows quickly upon release of the plugs

The Reason Underlying the Use of Ipecac

Because of the ease with which very small particles, or even quite large objects, gain access to the respiratory tract and because exudates

can accumulate within it, there arises the necessity for freeing the tract from such obstructions and irritants Macklin points out that three mechanisms are present within the respiratory tract 1) the cough reflex, 2) the action of the cilia, and 3) a wave motion said to resemble peristalsis These three often work together According to Gunn, the cough reflex functions in the upper airway, the cilia act as far down as the finer bronchioles, while "peristaltic' movements evacuate the entire tract, even including the airway terminals Thus, these activities overlap, the upper part of the airway having all three, the intermediate two, while the terminals would have only one mechanism for evacuation—namely that of "peristaltoid' motion The peristaltic movements are brought into play only under abnormal conditions(such as the ejection of masses of thick exudate from the respiratory lumina) The 'peristaltic" wave in the bronchial tree is said to resemble the reverse peristaltic wave in the digestive tract and the speed is too rapid to be accounted for by ciliary action Reinberg describes it as tracheal vomiting' and Bullowa and Gottlieb as 'bellows like" I prefer the former

It is obvious that ipecac, which causes nausea, retching and vomiting plus the irritation caused by the presence of the foreign material in the air passages, hastens and increases peristaltoid action This 'tracheal vomiting' releases the obstruction which, under ordinary circumstances, might not have been diagnosed for days Steam inhalation also enhances the release of thick dry plugs—because of its tendency to make mucous secretions thinner, and should always be used as an adjuvant

Opiates

I shall not dwell on the question of opiates, but I should like to state emphatically that the use of morphine in asthma is distinctly contraindicated Besides its inhibitory effect on the respiratory center, it also causes a bronchoconstriction I can see no reason for its use and believe that most deaths from asthma have been directly or indirectly due to its use This is supported by the study of Huber and Koessler

Histamine Histaminase and Antihistaminic Drugs

As to histamine and histaminase, I should also like to go on record as stating that not until it is more adequately proved that histamine plays a dominant role in asthma, shall I regard its use or the use of its antienzyme histaminase of significant value There is still too much mysticism surrounding the histamine concept of allergy, and its soundness is questioned by many That histamine may be increased in allergy is true, but

whether such an increase is in any way related to its causation is questionable It may merely be an end product of disturbed physiology

The so called antihistaminic drugs are of value in relieving nasal symptoms and urticaria They are of value in the treatment of hay fever but have been found wanting in the treatment of asthma They are contraindicated in severe asthma or status asthmaticus because of their marked soporific effect for which reason they may at times be as deleterious as opiates Furthermore the drying effects of these drugs on the already dehydrated mucous membranes of the bronchi would tend to aggravate the obstruction by the thickened secretions which are found in all cases of status asthmaticus

AMINOPHYLLINE

This drug has undoubted value in the treatment of asthma in childhood It is more useful perhaps in the chronic type of adult asthma It is best used rectally by suppository in one half strength and occasionally in full strength doses If injected intravenously or intramuscularly it should be given with 1 or 2 per cent procaine Its value lies in relieving arteriolar spasm and vascular congestion of the bronchi

Summary of the Management of Asthmatic Attack

(1) Give small doses of adrenalin (1 1000) 2 to 3 minims subcutaneously Repeat intracutaneously if necessary two to three times at intervals of 20 to 30 minutes

(2) If adrenalin is not effective give syrup of ipecac by mouth, 1 to 2 teaspoonfuls depending on the age of the patient and his response Follow with lukewarm water to promote emesis

(3) As adjuvants (a) give the patient an enema (b) remove patient from the bedroom into another room and prop him up in a chair, (c) be sure the patient is well protected then open windows and if not enough air is circulating in the room turn on the electric fan directing the current of air on the child (d) burn asthma powders Be sure that all persons attending the child assume a cheerful attitude to give the child encouragement

(4) Unmedicated steam inhalation is an important adjuvant

(5) If the attack is severe and prolonged the ipecac emesis should be followed by

(a) Ten to 15 per cent intravenous glucose by slow drip infusion (300 cc. for young children 500 to 1000 cc for older ones) This is an important procedure because it allays dehydration which is usually pronounced, and also reduces edema

(b) A rectal retention dose of some sedative, such as bromides (10 to 15 grains), phenobarbital (½ grain), chloral hydrate (2 to 7 grains) or ether in oil (1 to 2 teaspoonfuls in 1 to 2 ounces of a bland oil) The sedative may also be given by mouth in the form of triple bromides (5 to 15 grains), phenobarbital (¼ to ½ grain), amytal (½ grain), and/or acetylsalicylic acid (5 to 10 grains) This sedation may be repeated in two or more hours Aminophylline suppositories are of value

(c) Oxygen therapy is soothing and reassuring, but under no circumstances should the patient be put under an oxygen tent, for claustrophobia is very pronounced during severe asthmatic seizures It is for this reason that a gentle breeze from a fan is reassuring

(6) The status asthmaticus patient, having relieved himself of the obstructive plug and been soothed by the intravenous infusion of glucose and sedative, usually falls into a tranquil sleep The nurse or parent may be left to watch over the patient (he should not be left unattended) with an order for repetition of the ipecac and additional sedative if necessary

After the attack a salt free diet should be given, high in carbohydrates Plenty of liquids particularly cola drinks, and other sweet beverages should be prescribed The salt free high carbohydrate and liquid diet is supportive and increases diuresis tending to rid the body of offending allergens

All of these measures can readily be carried out in the home However, if it is deemed wise under certain circumstances to remove the child to a hospital there is no danger in doing it if the child is well protected Indeed, sometimes when children are moved to another room, or while they are being transported to the hospital, the asthma clears up This would indicate that an environmental factor is involved

The keynote, therefore, of the treatment of the asthmatic attack (probably with the exception of the emesis produced by ipecac) is gentleness of therapy, with the aim to correct the physiologic disturbance encountered

The long range program must focus on determining the etiological [illegible]

[illegible] with the incriminating foods or by immunization with injections of pollens inhalants and/or vaccines

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BRONCHIAL ASTHMA IN ADULTS

By LEON UNGER, M D

Definition

Bronchial asthma is an allergic condition, occurring at all ages, characterized by wheezing, dyspnea, orthopnea, and cough usually associated with rhinitis and partial obstruction of the lower air passages

Etiology

Three factors are important, especially the third

I *The Constitutional Basis* is unknown but *heredity* is important, with a positive family history of one or more allergic conditions in about 60 per cent of cases The predisposition to allergy is inherited, not necessarily the particular allergic disease Thus the grandfather may have asthma, the father hay fever, and the grandson may have "eczema" or asthma or both Similarly, members of the family often differ as to offending allergens, e g , one may be allergic to fish, another to house dust, a third to ragweed pollen The stronger the inheritance factor the earlier, as a rule, is the onset of asthma, this is especially true in children In instances of bilateral inheritance more than a third of the cases of asthma begin before the fifth year, as contrasted with about 15 per cent in the unilateral group and only 5 per cent in those with a negative family history There is, however, no proof that infants are passively sensitized from the mother through the placenta, and children are frequently sensitive to allergens other than those which affect the parents In those whose asthma begins after the age of 40 a history of allergy in the family is much less frequent and often entirely absent

II *Contributory Factors* are important but they rarely, if ever, initiate attacks of asthma They may aggravate or incite attacks in allergic patients who are also exposed to various substances listed under III to which they happen to be sensitive These contributing factors may be grouped as follows

(a) *Mechanical,* e g , chalk and certain other dusts

(b) *Chemical,* e g , fumes from tobacco, gasoline, molten metals, sulfur dioxide, and turpentine True allergy to tobacco probably occurs chiefly in those who work with the leaf, it is difficult to prove allergy to tobacco smoke

(c) *Physical allergy,* e g , light, heat, cold or pressure Asthma from these exposures is very rare though any one of these not infrequently causes urticaria like lesions

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(c) *Physical allergy,* e g , light, heat, cold or pressure Asthma from these exposures is very rare though any one of these not infrequently causes urticaria like lesions

(d) *Infections,* e g , ordinary "colds" bronchitis and sinusitis A cold should be defined as an acute condition very contagious, which usually begins with a raw throat followed by acute rhinitis with blocking and a nasal discharge which on examination usually contains many polymorphonuclear leucocytes (eosinophilia is usually absent from nasal smear) Fever may be present and symptoms usually last about a week The asthma, if it occurs usually begins about the second day It should be pointed out that unless there is a tendency to asthma such "colds" will not cause attacks of asthma Other members who are not allergic may "catch the cold" but they do not develop asthma

The above description of an infectious "cold" definitely separates it from allergic rhinitis which may come and go rather quickly or may persist for long periods is not contagious has no fever, and almost always shows eosinophiles in the nasal smear

(e) *Psychogenic* Nervous and psychic factors are very important predisposing causes but despite the claims of many writers that bronchial asthma is of nervous origin I am confident that this is not the case True *bronchial* asthma has never been proved to be due solely to such stimuli As in the case of the other contributory factors e g , mechanical and infectious emotions operate only in patients who have a basic allergic condition (usually inherited) and who are also exposed to certain allergens e g house dust or eggs For further discussions read *Bronchial Asthma* by Unger

The reverse should be noted Asthma itself is a frequent cause of nervousness The excitement of the attack with its dyspnea, wheezing cough and exhaustion induce apprehension and irritability and these are aggravated by epinephrin and ephedrin used for treatment The wonder is not that asthmatic patients are apt to be nervous but that one can live with some of them at all This nervousness disappears or lessens when the allergic cause of attacks can be removed

Despite the above resumé we must make every effort to minimize emotional factors which can aggravate an attack Such emotions are common and important

(f) *Endocrine* e g puberty menstruation menopause, pregnancy Here again are important predisposing factors Asthma may be aggravated by approaching menstruation and lessened when the flow starts Pregnancy usually lessens asthma though occasionally a patient will have asthma only during pregnancy The nervous factors incident to

menopause seem to increase asthma in some women But there is no proof that any endocrine influence can alone cause asthma

(g) *Miscellaneous* exhaustion, constipation, poor hygiene and lowered morale should be combatted After all, an asthmatic patient is an individual and must receive general as well as specific treatment

In summary, then, none of these contributory factors by themselves can initiate attacks of asthma or any other allergic condition They can, however, bring on or aggravate attacks in patients who are already allergic and who are exposed to one or more of the allergenic substances now to be discussed

III *Exciting Factors (Allergens)* In the preceding sections the hereditary and contributory factors were discussed, and it was emphasized that neither of these can cause symptoms unless there is also exposure to one or more exciting substances known as antigens, allergens or atopens

Most allergens contain protein, hence the term "protein-sensitization tests " But certain non protein substances can cause attacks e g, drugs (aspirin, quinine) The carbohydrate fraction of a substance may be important, but the allergenic properties almost certainly lie in the protein fraction

The *allergic threshold* or equilibrium is the barrier which prevents symptoms in sensitized persons Once this threshold has been ove as by exposure to an overwhelming amo occur It is difficult, if although injections of step in this direction We therefore use the term "hyposensitization rather ng substance constitute a than "desensitization

There is a *time interval* between the first exposure to the specific aller gen and the onset of symptoms When exposure is massive, as with workers in a bakery or grain mill, the interval is apt to be shorter, but with substances like pollen the exposure is intermittent and the onset is usually delayed or may not occur at all In addition, exposure must be adequate

Cooke's postulates to prove that a substance can cause allergic symptoms are 1) the substance must give a positive local reaction or must be able to cause clinical symptoms, 2) the patient must be known to have been exposed to this substance

Allergens can cause asthma by inhalation, ingestion or injection Some allergens can act in more than one way, e g, wheat flour can cause asthma by inhalation and dermatitis by contact Some allergens can

cause more than one set of symptoms, e g, egg can give rise to asthma, rhinitis, atopic dermatitis (eczema), migraine, urticaria, and gastro-intestinal allergy

The chief allergens in bronchial asthma and rhinitis are

A Inhalants

(1) Pollen of trees, grasses, weeds

(2) Spores of fungi molds, smuts, rusts, yeasts

(3) Animal hair, dander, feathers

(4) House dust—extremely important

(5) Cereals flour of wheat, corn, rye, etc

(6) Seeds of cotton, kapok, flax, etc

(7) Miscellaneous orris root (cosmetics), pyrethrum (insecticides), sawdust, karaya gum (wave sets), certain powdered drugs, insects, etc

(8) Occupational dusts, e g, farmer, miller, furrier, baker, upholsterer, domestic

B Ingestants

(1) Foods egg, wheat, milk, fish, pork, etc

(2) Drugs, especially aspirin

C Injectants

(1) Overdose of extracts used in hyposensitization especially pollen

(2) *Drugs, e g, morphine, arsphenamin, vitamins*

(3) Serums, e g, tetanus and diphtheria antitoxin

D Miscellaneous Mode of action not too clear

(1) Bacteria and their products

(2) Parasites e g, ascaris and taenia

(3) Silk

(4) Physical agents, e g, cold or heat?

The reader who wishes more information about any of the above is referred to textbooks on allergy A few comments follow

The *inhalants* are undoubtedly the main factors in attacks of true allergic bronchial asthma and rhinitis Pollen causes seasonal hay fever, approximately 40 per cent of all untreated hay fever sufferers sooner or later develop bronchial asthma While pollen differs in different sections, symptoms are due chiefly to the light, buoyant, wind carried pollen of weeds, grasses, and trees Pollen of flowers is carried by insects and is of little consequence Symptoms of hay fever are directly proportional to the amount of pollen in the air, but pollen asthmatics frequently suffer

during a thunderstorm or on other damp days when the pollen count is low

The importance of spores of fungi is becoming increasingly recognized Fungi occur all over the world although not all are found in all places The allergenic fraction of molds lies in the spores, extracts of mycelia are unimportant Clinically they resemble pollen in many respects, especially in that symptoms are directly proportional to the mold spore count Alternaria and hormodendrum are the most important molds in some sections, but penicillium, aspergilli and other molds predominate in other parts of the world Grain smuts are important in asthmatic patients from the farm or flour mill Yeasts and rusts occasionally cause asthma

House dust is one of the main causes of asthma It is a grey powder which exudes from aging bedding and soft furniture but its exact nature is unknown There is some disagreement as to whether it does or does not contain a specific allergen, but it has been proved allergenic by skin and transfer tests, by constitutional reactions from overdosage, by anaphylaxis experiments in animals, and especially by relief of symptoms by avoidance

Animal danders, especially from horses, cats and dogs, frequently cause asthma and rhinitis, with brilliant results by avoidance, supplemented in some cases by hyposensitization Those allergic to horse dander must be given tetanus and diphtheria toxoid else any future antitoxin is very apt to cause anaphylactic shock

The other inhalants are less important but as a group they cause symptoms in many patients Cottonseed protein is a potent allergen found especially in mattresses Kapok should be avoided by all allergic individuals Orris root is becoming of less importance because cosmetic manufacturers now usually omit it, it still occurs in perfumes and gin

Farm dusts are mixtures of cereals, molds, rusts, smuts, insects and other substances Excellent skin test reactions are often found in patients from farms, with good results on avoidance plus hyposensitization.

Foods can also cause bronchial asthma and other allergic conditions Since ancient times it has been known that certain foods cause peculiar symptoms in certain individuals, "What is one man's meat is another man's poison" Eggs, wheat, milk, and corn are probably the most important in this respect, although other foods can also cause attacks Foods are probably more causative in infancy and childhood than in adult life Antigenicity is lessened by heating, less sensitive patients can

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eat moderate amounts of cooked foods to which they are allergic. If a person is allergic to a food he is also apt to be allergic to other members of that food's genetic family, e g, the legumes.

Drugs are rather infrequent causes of asthma, but if a patient states that aspirin brings on an attack the wise physician will give strict orders to avoid aspirin and all aspirin containing drugs, e g, "Alka Seltzer" Terrific attacks of asthma, even death, have resulted from carelessness in this respect, and the aspirin sensitive patients frequently have severe asthma

Overdosage of extracts during hyposensitization may cause asthma, rhinitis, and urticaria or even shock its occurrence is greatly diminished by care during treatment

The role of bacteria is still hotly debated Some believe that they act as a primary allergen Others deny this, while conceding the great importance of bacterial infection in asthma and the good results often obtained by the use of bacterial vaccines

Incidence of Asthma

It occurs in all races all over the world in approximately 0 5 per cent of the population There are about 500 000 to 1,000,000 cases in the United States, but statistics are not too reliable because the condition need not be reported The mortality is low but the morbidity is high There is a slight predominance in males Asthma occurs at all ages, but is especially frequent in the first decades of life, these periods also offer the best prognosis if allergy management is promptly begun

TABLE I

SEX AND AGE OF ONSET OF 459 CASES OF BRONCHIAL ASTHMA

Age at Onset	Paroxysmal		Chronic	
	Male	Female	Male	Female
0-9	95	49	13	25
10-19	16	28	12	16
20-29	18	32	5	17
30 39	17	14	9	14
40 49	10	14	15	14
50-59	3	2	7	10
60-69			2	2
TOTALS	159	139	63	98

Environment is very important, especially as regards exposure to large amounts of house and occupational dusts pollens, molds, and animals. Social status climate, altitude and seasonal variations probably

act by lessening or increasing exposure to allergens, but they may also influence respiratory infections

To aid in discovering the cause of asthma a chart on its relative relationship to occupation follows This is only a suggestive guide

TABLE II

OCCUPATIONAL ASTHMA AND RHINITIS

OCCUPATION	CHIEF ALLERGENS
Aquarium Supplies	Derris root, Water flea (fish foods)
Bakers	Wheat corn, rye buckwheat, spices
Barber (and Beautician)	Orris root, henna dyes, Karaya (Indian) gum, tragacanth, flaxseed, quince seed, hair, sheepwool, wool grease, oil of citrus group, essential oils
Bedding	(1) Feathers chicken, duck, goose swan, pigeon, turkey (2) Animal hair horse, rabbit, goat, cow, hog, cat, sheep (3) Cottonseed kapok, silk floss, flaxseed (4) Straw, corn husks, wood shavings
Brushes	Animal hair cow, hog, horse goat, sheep
Butchers	Hair cow, sheep, hog, rabbit Insecticides, preservatives Boxwood (sawdust) on floor Physical allergy (cold refrigerators)
Canners	Peas and beans infested with Indian meal moth
Clothing	Dyes Hair horse, goat, cattle, cat, dog, rabbit, camel, sheep wool
Exterminators	Pyrethrum orris root, chemicals (D D T)
Farmer	Vegetables (tomato workers Cladosporium) cereals etc Livestock and cats, dogs, rabbits etc Poultry Corncockle Chicken coop mites molds smuts feed (Kamala) Pollen, molds corndust (smut)
Florist	See Horticulturist
Flowers (artificial)	Feathers chicken, duck, goose, swan, turkey Silk Dyes
Flour Mill Workers	Grain smut and rust Wheat, rye, corn, buckwheat Molds, mites, pollen
Furniture	See Bedding
Furriers	Dyes Insecticides, sawdust (boxwood), furs Fumes from cleaning fluids e g naphtha Imitation furs cat, dog, rabbit, goat cow
Gloves	Hair rabbit, horse, sheep, goat, cat
Grain Elevator Operator	See Flour Mill Workers

still further decreases the amount of available oxygen and adds to the severity of the asthma This edema is easily demonstrated at bronchoscopy, the plugs are frequently coughed up and seen grossly and under the microscope, and necropsies have repeatedly confirmed the importance of edema in bronchial asthma Mucous glands frequently secrete an excessive amount of mucus in asthma and this increases the trouble

From ancient times most men recognized the spasmodic nature of asthma, and many thought that this was due to a spasm of the bronchial tubes The theory of bronchospasm has lost most of its earlier advocates, but spasm may play a part Alexander says, "It is probable that since vagus (parasympathetic) stimulation, which is the nerve impulse that initiates an attack, causes all three lesions, no one, but all, play a role In the earlier stages of the disease, edema and bronchial constriction are probably the most important factors since the mucous glands are small and the production of mucus scant In long-standing asthma, increased, thick, tenacious mucus is probably the most important factor in bronchial obstruction"

In chronic asthmatics, as Huber and Koessler showed, *hypertrophy of the bronchial muscles* may also occur and add to the obstruction, although it cannot be the whole cause

Some workers believe that *histamin* or a histamin like substance is elaborated during attacks of asthma by interaction of allergen and antibody in or at the sensitized bronchial cells Despite a large number of experiments this theory has not been proved There is much evidence against this hypothesis For one thing, the new so-called antihistaminic drugs like benadryl and pyribenzamine have been singularly ineffective in all but the mildest cases of asthma

PATHOLOGY

Deaths during attacks are uncommon but they do occur, especially in older patients with chronic asthma Injections of morphine not infrequently precede exitus, and this drug *should never* be used in bronchial asthma because it lessens the cough reflex and slows respiration, thereby increasing anoxia In a series of 459 cases over a 20 year period there were 48 deaths and the importance of morphine is shown in the following table

TABLE III

CAUSES OF DEATH IN BRONCHIAL ASTHMA

1	Asthma main or sole cause	21 cases*
2	Asthma a contributory factor	16 cases
3	Other causes (asthma not a factor)	11 cases

*Morphine known to have been injected prior to death in 6 of these patients

Necropsies in bronchial asthma reveal

(1) Emphysema with pressure of enlarged lungs against the chest wall, with overlapping of the heart

(2) Localized areas of atelectasis—those areas may alternate with emphysematous tissues to give a peculiar "doughy" feeling

(3) Thickening of the bronchial muscles in chronic cases

(4) Increased secretion in the walls and lumina, with many mucous plugs

(5) Widespread eosinophilia in the walls, in the lumina, and, in the plugs

(6) Thickening and hyalinization of the basement membrane of the bronchi

(7) In many cases there are also one or more complications, e g , chronic infectious bronchitis or pneumonitis, bronchiectasis, sinusitis, and nasal polyposis Less frequent are spontaneous pneumothorax and mediastinal emphysema Other conditions may also coexist, e g , carcinoma or tuberculosis but they are uncommon in true bronchial asthma The heart is rarely affected in allergic asthma, although heart disease and asthma may coexist

In paroxysmal asthma these changes may be reversible, but they are usually irreversible in chronic asthma with emphysema The many necropsy reports in asthma are summarized by Unger, together with details of five cases in which death occurred in patients with uncomplicated bronchial asthma

Symptomatology

Dyspnea, orthopnea, wheezing and cough are the main symptoms in bronchial asthma These may occur in attacks (paroxysmal asthma) with reversible changes and a good prognosis, or symptoms may be constant (chronic asthma) with a less favorable outlook because the pathological changes are apt to be beyond repair

In patients who have attacks of asthma, symptoms are absent in the free intervals, but in many who think they are entirely symptom free between attacks questioning may reveal a little dyspnea on such exertion

as would not affect normal people, and a little wheezing may be heard with the stethoscope.

In *paroxysmal asthma* symptoms may be mild to severe In the mild group there is a little dyspnea, especially on exertion, a little cough, some wheezing, best heard with a stethoscope, and perhaps some expectoration. Fever is rare in adults, common in infants and young children A little ephedrin or epinephrin usually suffices. The patient "carries on"

In the moderate cases the symptoms are more severe The patient may be in bed, with orthopnea, wheezing and dyspnea A little exertion is possible The attack may last longer but usually responds to one or more injections of epinephrin and/or aminophyllin

In the more severe cases symptoms may start slowly or suddenly and the patient becomes bed ridden and gasps for breath, cyanosis and tachycardia are common Expiration is usually prolonged, and wheezing can usually be heard for long distances Such attacks may last from a few hours to about four days, but the patient makes a complete or almost complete recovery and is well until the next spell

In *chronic asthma* symptoms also range from mild to severe Many patients wheeze and cough every day but manage to keep on with their work, provided the work demands little exertion Some patients are more or less completely incapacitated

Status asthmaticus is the most severe stage of chronic asthma Suffering is severe, with loss of weight, strength and morale An infectious complication is often present, e g , bronchitis or pneumonitis, as evidenced by clusters of crepitant rales, low fever, leucocytosis and increased sedimentation rate In some of these 'infectious asthmas" the chest film may show some mottling Rapid pulse, cyanosis, excessive perspiration, and marked dyspnea and orthopnea are co ... eating is an exertion
which increases ... Status as ... proper treatment,
can almost alw ... ome althoug ... for several weeks
or even longer ... occur but is ... unless morphine is

during the attack is always more or less reduced Various biochemical studies have shown no significant abnormalities with special reference to blood calcium, phosphorus potassium sodium and magnesium levels Blood sugar level is usually normal or low, there is a tendency to gastric hypo acidity

Diagnosis

The diagnosis involves three considerations

I Is bronchial asthma present?

II What complications if any exist?

III What causes the attacks?

DIRECT DIAGNOSIS

The diagnosis of bronchial asthma is usually relatively easy and is based on

(1) History of attacks of wheezing dyspnea orthopnea and cough In paroxysmal asthma the patient states that he is normal between spells In chronic asthma symptoms are more or less continuous often with exacerbations

(2) Examination wheezing and prolonged expiration are usually present over all parts of both lungs The heart is often small and heart tones are frequently best heard in the epigastrium (because the heart is often overlapped by emphysematous lungs) Fluoroscopy usually reveals an elongated or normal sized heart and a low diaphragm with lessened excursions In chronic asthma increased intercostal spaces and hilar and bronchial markings are common

(3) Eosinophilia is usually present in the blood (up to about 20 per cent) and often much higher in the sputum (up to 100 per cent) A Wright or similar stain should be routine with sputum as well as the Ziehl Neelsen stain for tubercle bacilli A high eosinophile count in sputum is also of great diagnostic importance in allergic bronchitis a condition which may precede true bronchial asthma but in which wheezing and dyspnea are absent Nasal allergy is often associated with allergic asthma and nasal smears usually show eosinophiles in such cases

(4) Relief from epinephrin and/or aminophyllin This usually occurs in asthma but in certain cardiac conditions these drugs can also lessen dyspnea

(5) Positive skin tests clinically corroborated (see below)

(6) Allergy in the family or other allergic conditions in the patient

It must be emphasized that any one of these findings can occur in

non allergic conditions The more of the above findings, however, the more certain is the diagnosis of bronchial asthma

COMPLICATIONS

Emphysema is probably always present with chronic asthma The alveoli enlarge because there is incomplete blocking of the lower respiratory tract Permanent deformities of the chest frequently follow, these vary according to the age of onset and the severity of symptoms The sternum may be indented in young children, older children tend to develop pigeon breast and adults the barrel type Breath sounds are distant Heart tones are frequently best heard in the epigastrium because the enlarged lungs may overlap the heart Once emphysema has occurred it rarely disappears, if asthma persists the emphysema may progress to the point of complete disability

Infectious complications occur rather frequently, especially in chronic asthma These include bronchitis and pneumonitis—either of these or both may be associated with fever and they are usually readily controlled by penicillin or other antibiotics When an asthmatic patient has fever, leucocytosis increased sedimentation rate and clusters of crepitant rales in addition to wheezing he almost certainly has a complicating infection in the lungs and should receive antibiotic therapy as well as measures directed toward asthma itself Infectious sinusitis is infrequent in asthma.

Bronchiectasis may also be present, although asthma is not necessarily the cause It should be suspected if the morning sputum is profuse, especially if it is fetid, or if produced by change in position or if hemoptysis occurs The diagnosis is confirmed by x ray films taken after instillation of iodized oil The dilatations may be tubular or saccular and are especially frequent in the lower lobes Clusters of moist rales are usually heard

The exact relationship between bronchiectasis and bronchial asthma is not clear The two can occur together, possibly independently Watson and Kibler from Arizona state that in 90 per cent of their cases of bronchiectasis the diagnosis of allergy was made from the history, *positive skin tests*, associated allergic conditions and by the presence of at least 10 per cent of eosinophiles in the nasal or bronchial secretions They believe that the process begins with a basal allergic bronchitis followed by atelectasis and then dilatation of bronchi *In our experience* this high percentage does not occur, we rather agree with Bullen who found bronchiectasis in only 7 75 per cent of his asthmatic patients

Bronchiectasis is a fairly common condition and wheezing occurs in many cases Not all are allergic, however, as anything which partially obstructs the respiratory tract can cause wheezing It is my opinion, although I cannot prove it, that bronchial asthma rarely causes bronchiectasis, when they occur together coincidence is more likely If the two do occur treatment must be directed against both conditions (see below)

In a recent article, Mallory points out that in 60 cases of bronchial asthma with chronic functional narrowing of bronchi bronchiectasis was so exceptional as to appear coincidental Furthermore, in the great majority of bronchiectatic lungs there is no evidence of narrowing of the bronchial tree proximal to the areas of dilatation Mallory believes that only the assumption of a primary infectious bronchitis with secondary atelectasis, with or without pneumonitis, can explain the occurrence of bronchiectasis Congenital malformations and bronchostenosis are unimportant causes

Atelectasis is undoubtedly very common in bronchial asthma, but most areas are small and their presence can be proven only at necropsy It follows complete obstruction of a bronchiole If a large bronchus is obstructed the condition is termed "massive atelectasis" (formerly known as "massive collapse") A whole lobe may become airless and in asthma this is usually due to a mucous plug, with relief on expectoration of the plug or after removal through a bronchoscope In such a massive obstruction the breath sounds are usually absent on the affected side and the mediastinum is pulled toward that side, as shown on examination and x ray

Spontaneous pneumothorax is not infrequent An emphysematous vesicle or a lobule may rupture from overdistension during an attack of asthma Pain, dyspnea, orthopnea and cyanosis may occur suddenly or slowly usually depending on the size of the opening Tympany and absent breath sounds occur on the affected side, and the heart is pushed toward the opposite side Recovery is usual, though death has resulted

Subcutaneous emphysema is less frequent but more dangerous It can occur with spontaneous pneumothorax and is due to the rupture of one or more air sacs at the hilus or periphery, the air migrates into the mediastinum and neck and may reach the face Audible crepitation on pressure is diagnostic, and an x ray film helps

Attacks of asthma may be so severe that one or more ribs may be fractured Localized pain suddenly occurs, especially on deep breathing,

and localized tenderness and swelling are usually present There is seldom any displacement and healing is rapid Adhesive taping is advised

Nasal polyposis is very common in chronic asthma The nasal mucosa becomes edematous If the condition persists, the weight of the fluid forces the mucosa to hang down more and more till the grape like pale tissue can be seen The polyps may be small or so large as to block the nostrils and even to reach the exterior nares In all cases there is coincident polyposis of one or more of the accessory nasal sinuses, and this explains why removal of nasal polyps is frequently followed by the later appearance of other polyps which have emerged from the sinuses Nasal polyps are almost certainly the result of allergy, and if they are not too large they may disappear when proper allergy measures are carried out Nasal smears in such cases almost always reveal a high percentage of eosinophiles In some patients polyps cause asthma by a trigger mechanism by pressure, with relief on removal of the polyps

The *heart* is rarely affected by bronchial asthma Numerous studies have been made on the effect of chronic asthma on the cardiac structures—clinical, electrocardiographic, and at necropsy From these we can conclude that cardiac decompensation rarely follows bronchial asthma, mild or severe, paroxysmal or chronic, unless the patient also has an associated cardio-renal disease, e g , hypertension, rheumatic, syphilitic or congenital heart disease, or nephritis Most asthmatic patients have as good or better hearts than do normal persons of equivalent ages

This optimistic attitude has also been expressed by many other allergists In 1839 Andral said that asthma "is a brevet of long life" Oliver Wendell Holmes agreed that asthma "is the slight ailment that promoted longevity Bray says that "Many asthmatics pant on to a good old age' Alexander believes that during an attack the quantity of blood which enters the right heart is diminished, thereby actually sparing the heart These opinions are confirmed by Criep and others

Several articles have appeared which challenge this optimistic point of view Dublin and Marks say that the mortality in asthmatics is about two and one third times the normal, but their figures are taken from death certificates which are not always accurate In some of their cases of "death from asthma' organic heart disease (cardiac asthma) was probably responsible for death rather than bronchial asthma

From the electrocardiographic point of view, however, chronic asthma does tend to change the axis to the right, as shown by Unger,

Colton and Ziskin, and others Right axis deviation is common in such cases Yet, clinically, there is absolutely no tendency to decompensation unless as stated, there is an associated cardiorenal disease

Cor pulmonale, too, is extremely rare in uncomplicated bronchial asthma This author has never seen such an outcome unless the patient had some other pulmonary condition, e g , severe bronchiectasis silicosis, cystic lungs, fibrosis, or kyphoscoliosis

Since asthma occurs at any age it can, of course, be associated with any other condition Tuberculosis is rather rare in asthma, though the two can occur coincidentally In addition, chronic pulmonary tuberculosis can cause narrowing of the respiratory tract with consequent wheezing which is usually unilateral and more or less constant Diabetes mellitus and syphilis are also infrequent in asthmatics Heart disease is more commonly associated, especially hypertension, coronary disease, and valve involvements Carcinoma of the lung not infrequently is present with true asthma

CAUSE OF ATTACKS (SPECIFIC DIAGNOSIS)

This is often discovered very easily but in some cases every diagnostic method is necessary, even then there are cases in which the cause of attacks cannot be found The more thorough we are the fewer are the failures in this respect

1 Histories should be taken very carefully The patient should be encouraged to talk without interruption The detective nature of the inquiry should be explained The circumstances of all of the attacks should be drawn out, yet leading questions are to be avoided, if possible The season, the time of attacks, the exposures, etc are to be noted on the history sheet It is especially important to classify the symptoms as paroxysmal or chronic, this helps as regards prognosis and treatment Almost every true asthmatic wheezes, coughs, and has dyspnea and orthopnea If there is no orthopnea the diagnosis of bronchial asthma at once becomes uncertain (except in infants) Fever is rare in uncomplicated asthma (except in children) Expectoration is usually difficult in asthma especially when the attack begins if it is easy and profuse bronchiectasis is more likely

When the patient has finished his story, we ask specific questions e g , what brings on the attacks? What about idiosyncrasy to foods or drugs? Any periods of freedom and if so, why? Space will not permit a list of all possible questions but the patient's home and occupational exposures are carefully brought out as possible causes of attacks The his

tory of previous or associated or family allergies is taken, and the information regarding past illnesses, habits etc, are obtained A good history may be diagnostic, e g, exposure to horses or flour or asthma after eating eggs

2 Further information may be obtained by having the patient avoid suspected allergens, e g a dog or wheat or feather pillows If symptoms clear on avoidance they may return when exposure is tried Such clinical tests are even more corroborative than are positive skin tests

3 Further information may be obtained from correlation of the patient s symptoms with the atmospheric pollen or mold counts If asthma and/or hay fever occur each August and September when rag weed pollen is in the air, the cause of the attacks is usually self evident and in almost all these cases positive skin tests are obtained with rag weed pollen extracts Molds too may cause seasonal symptoms as with pollen

4 *Skin tests* It is necessary to test for all substances which might conceivably be important If complete tests are not carried out important causes may be missed One cannot rely on the history alone to determine what tests to do e g one allergic to cottonseed rarely realizes this fact until informed by the skin test The practice of doing 20 to 30 tests on a child and informing the parent that skin tests have been carried out is reprehensible —it is of no more value than is the incomplete physical examination Each substance should be tested for individually group tests may fail because of dilution

(a) *Scratch tests* are simple and without danger Sixty or more can be done at each sitting and the total number of materials is approximately 300 The extracts are in liquid or powdered form we scratch with a cataract knife

(b) *Intracutaneous (intradermal) tests* should be done in those patients in whom scratch tests have failed to give sufficient information The needle tests may be dangerous unless the scratch test for the same material is negative Severe reactions including death continue to occur in patients in whom this precaution has not been observed No one can accurately estimate in advance the degree of sensitivity of that patient to the particular allergen which caused the reaction The intracutaneous method is more delicate but requires aseptic technique, sterilized solutions syringes and needles One drawback is that it is more often associated with false positives than is the scratch method

(c) *Passive transfer* (Prausnitz Kustner) is indicated when direct testing is unreliable or impossible as in severe dermatitis or dermographia Its usefulness is chiefly in the experimental field

(d) *Ophthalmic and nasal testing* may be valuable in allergy to pollen, molds, and other inhalant substances, but these methods should be tried only when scratch and intradermal tests are negative

Skin testing is not a laboratory procedure Its results must be correlated with the history of exposure and clinical trials A positive reaction does not prove that the substance is the cause of present symptoms; it may indicate past or potential sensitivity A person may also be allergic to a substance and yet skin tests for that substance may be entirely negative The condition of the skin, too, plays a part in interpreting the reactions

Nevertheless, despite some shortcomings, skin tests constitute a very important approach to discovery of the cause of symptoms They must be carefully and thoroughly carried out, and the results must be correctly interpreted They are successful in at least 75 per cent of all cases of bronchial asthma

In doubtful cases of food allergy much useful information can frequently be obtained by elimination diets and feeding trials Food diaries are also helpful

Differential Diagnosis

The diagnosis of bronchial asthma is usually rather easy, but the condition must be differentiated from all other causes of dyspnea, wheezing, orthopnea and cough These can be placed in two groups, i e, with and without obstruction of the upper airways

1 *Obstructive conditions* in the upper air passages are frequently associated with stridorous breathing (inspiratory wheeze plus dyspnea) In bronchial asthma the expiratory wheeze is almost always more evident than the inspiratory Among obstructive lesions may be mentioned

(a) Severe nasal deformities with resultant snore

(b) Large tonsils and adenoids, occasionally

(c) Laryngismus stridulus in infancy (some believe this may be a first symptom of asthma)

(d) Localized tumors, e g, carcinoma of the trachea

(e) Laryngeal diphtheria

(f) Paralysis of the vocal cords, from any cause

(g) Lesions which press on the larynx, trachea or primary bronchus, e g, enlarged thymus, substernal goiter, retropharyngeal abscess,

aneurysms, enlarged lymph nodes (Hodgkin s disease, leukemia tuberculosis etc) and various types of tumors especially carcinoma

(h) Foreign bodies as emphasized by Chevalier Jackson and his All is not asthma that wheezes

In all of the above lesions the correct diagnosis should not be too difficult A thorough history and examination including x ray and laboratory tests should be diagnostic There is usually no history of allergy in the patient or in his family wheezing if present, is usually chiefly inspiratory eosinophilia is uncommon but it can occur In a recent patient with carcinoma of the tracheal carina there was 100 per cent eosinophilia in one sputum specimen Wheezing was chiefly inspiratory and openings to both main bronchi were almost completely closed by squamous celled carcinoma as shown by biopsy Eosinophilia can also occur in other non allergic conditions e g Hodgkin s disease and leukemias

2 *Nonobstructive conditions* may al o simulate bronchial asthma In these dyspnea is more prominent than wheezing —nevertheless they may cause confusion especially if the patient also has bronchial asthma Any cardiac or pulmonary disease can also lead to dyspnea as can anemias and some functional disorders

(a) ' Cardiac asthma is a term given to a paroxysmal condition probably due to sudden failure of the left ventricle ' Acute suffocative pulmonary edema or ' acute cardiac dyspnea are better terms This is purely a cardiac condition but is often confused with bronchial asthma as both occur in spells and wheezing is present in both The similarity of names has caused more confusion than similarity of symptoms

The main features of cardiac asthma are the older age presence of cardiac disease involving the left ventricle (hypertension coronary disease, luetic aortic regurgitation or nephritis) and especially the finding of many moist rales at both lung bases The wheezing is coarse and not at all like the fine musical high pitch characteristic of bronchial asthma

The differential diagnosis is emphasized because lives can be saved by giving epinephrin to the patient with bronchial asthma and morphine to the individual with the much more serious cardiac asthma (see table)

TABLE IV

	BRONCHIAL ASTHMA	ACUTE CARDIAC DYSPNEA (CARDIAC ASTHMA)
F	allerg c)	Paroxysmal dyspnea (card o-renal)
H story	s	Attacks very few

Obstruction lower air passages	Pulmonary edema (failure left ventricle)
Onset in early life	Onset after 40, usually
Allergy in patient and family	Hypertension, coronary disease aortic regurgitation chronic nephritis
Eosinophilia blood and sputum	Absent
Wheezing, prolonged expiration all over both lungs	Moist rales, especially at bases, some wheezing
Warm perspiration	Cold clammy skin
Condition usually good	Often in shock
Heart usually small	Heart dilated
Pulse good	Pulse often thready irregular
No fear of death	Fear of death
Epinephrin or aminophyllin usually gives relief, morphine dangerous	Morphine best also digitalis and venesection epinephrin doubtful
Positive skin tests, usually	Negative
Elimination of cause gives relief, often complete	Rest in bed, etc, prolongs life
Circulation time normal	Circulation time prolonged

(b) *Fibroid tuberculosis* may also cause wheezing and some dyspnea, but the wheezing is localized and apt to be more or less constant Epinephrin and aminophyllin are usually ineffective Showers of crepitant rales are usually associated and the correct diagnosis should be made by these findings plus the presence of fever, tubercle bacilli in the sputum, distinctive x ray findings, and the absence of allergic features Tuberculosis and true bronchial asthma occasionally co exist

(c) *Silicosis* is a chronic progressive disease which is characterized by irritation of the bronchi from inhalation of various kinds of silica Connective tissue is excessively formed and this tends to obliterate bronchial lumina Wheezing and dyspnea result and may gradually become so extreme as to cause complete incapacity The correct diagnosis is usually evident by the history of exposure to silica, the occasional wheeze, the tendency to cor pulmonale, the absence of allergic involvement X-ray films, especially in the nodular type, are very helpful

(d) *Asthmatic bronchitis* may occur at any time of life but is especially common in the extremes of age It is characterized by attacks of cough, wheezing, fever, leucocytosis, and an increased sedimentation rate The attack usually clears in a few days There is some argument as to whether or not this is a forerunner of true bronchial asthma Asthmatic bronchitis probably can be divided into two groups (a) those which are allergic from the start and have the characteristic allergic features, e g, family history of allergy, response to epinephrin, eosinophilia in the blood and sputum, and positive skin tests In this group typical attacks of bronchial asthma will usually follow unless prompt preventive measures are instituted (b) In the other group infection, not allergy, is the main factor and true bronchial asthma rarely follows It is not al-

ways easy to differentiate these two groups when the attack occurs,—the correct diagnosis may require some time and study, but allergy surveys should be made in both groups as severe asthma can often be prevented

(e) *Bronchiectasis* has been mentioned above It may occur with or without asthma It is characterized by attacks of cough with much sputum, with or without dyspnea and/or wheezing, showers of moist rales localized in one or more areas, mild fever and hemoptysis in some, and distinctive findings by x ray after instillation of iodized oil In those cases in which bronchial asthma coexists eosinophilia in the sputum is usually found

(f) *Functional (sighing) dyspnea* is not rare A few individuals take deep sighing breaths, they feel that they are not "getting enough air" If the deep breathing continues for some time tetany may result Cure is usually easy the patient is shown how to breathe normally

(g) *Carcinoma of the lung* occasionally leads to confusion in diagnosis, but if the tumor occurs in a large bronchus wheezing, cough, and dyspnea may be rather marked and mistakes in diagnosis are common This constitutes a great tragedy because lobectomy or pneumonectomy can successfully be carried out in many of these cases if the diagnosis of carcinoma is made early enough The presence of localized wheezing, of persistent cough especially in an older patient, of possible hemoptysis, and the absence of evidence of allergy should make one suspicious Examination by bronchoscopy and x ray is diagnostic in many cases, even in the early stages when surgery is feasible When the later findings of carcinoma ensue, e g, loss of weight and strength, fever and severe hemoptysis, surgical intervention is usually *too* late Moore's differential table is good,—but no one of his points is infallible

TABLE V*

CARCINOMA LUNG	BRONCHIAL ASTHMA
1 Usually no allergy in patient or family	1 Allergy usually present
2 Onset after 45, usually	2 Onset before 45, usually
3 Cough precedes wheeze by several months	3 Cough usually comes with or follows the wheeze
4 Wheezing localized	4 Wheezing generalized
5 Diaphragm arched	5 Diaphragm apt to be flattened
6 No eosinophilia in sputum	6 Eosinophilia usual in sputum.
7 Hemoptysis often	7 Hemoptysis rare
8 Marked weight loss and rapid down hill course	8 Weight and course about same

*From Moore, M W Carcinoma of the Lung with Asthmatic Symptoms, Ann Allergy, 3 271, 1945

(h) *Loeffler's syndrome* is characterized by transient pulmonary consolidations with eosinophilia, wheezing is often present, and in some cases the symptoms are very suggestive of asthma There is strong evidence for the assumption that the condition is allergic Eosinophilia may be extreme, up to 66 per cent as emphasized by Loeffler, or even higher Symptoms usually clear spontaneously, the x ray helps in showing the consolidations and their disappearance, skin tests may be positive

(i) *Tropical eosinophilia* may be closely related It "occurs chiefly, but not exclusively, in the tropics, especially in India The chief symptoms are an insidious onset, with malaise, low grade fever, headache, and unproductive cough wheezing and dyspnea are often associated Leucocytosis (up to 60 000) and marked blood eosinophilia (up to 89 per cent) are striking features Chest x ray films usually show fine mottling in both lungs One to six intravenous injections of neoarsphenamine or other arsenical products cause prompt relief with disappearance of leucocytosis, eosinophilia, and the so called asthma No causative organisms have been found, according to Unger and Gordon

(j) *Periarteritis nodosa* may also be related This condition is usually, but probably not always, fatal It seems to have some relationship to allergy in general and to asthma in particular It is an arterial disease of small and medium sized vessels, with periarterial infiltration by eosinophiles polynuclear cells and lymphocytes Occlusion frequently results and may occur anywhere in the body, including the lungs Eosinophilia may reach 84 per cent, but may be absent The exact cause is unknown but the clinician should suspect this disease in all severely ill patients, especially those who are allergic Examination of blood vessels in a piece of muscle (calf) may be diagnostic.

(k) *Chronic cardiac decompensation* may also confuse, especially if it occurs along with bronchial asthma in an older patient who has some associated cardio renal condition Nocturnal insomnia may occur before edema of the feet, or enlarged liver, moist rales at bases, etc

Treatment of Bronchial Asthma

I Preventive Measures

(a) Children of allergic parents are apt to develop allergic symptoms, including asthma They should therefore be shielded from the most common causes of attacks, e g , dogs cats, orris root (certain cosmetics), feathers (pillows, comforters), fuzzy toys, excessive quantities of house dust, and large amounts of pollen as frequently found in vacant

lots and in certain play camps—(they should be tested with pollen extracts before going to such camps) New foods should be introduced singly to see if symptoms result Cooked foods are less allergenic than raw foods, raw egg may be disastrous. The house *should be spic and span*, and a good vacuum cleaner, with attachments, is strongly advised, whisk brooms only spread dust

(b) Mild allergic symptoms are apt to occur early in these children, e g, "eczema,' frequent 'bronchitis," hay fever, rhinitis, wheezing, or various gastrointestinal "upsets" Complete skin tests should be done at once, followed by elimination of offending allergens Hyposensitization may also be necessary and should not be delayed It is easier to prevent chronic asthma than to cure it Children rarely "outgrow asthma

(c) Allergic individuals and these children of allergic parents should avoid "dusty occupations (see Table II), especially farmer, baker, furrier, grain mill worker, upholsterer, and domestic

(d) Allergic individuals should not intermarry,—this advice is *easier to give than to follow*

(e) Hygienic measures are important, especially as regards avoidance of persons with ordinary 'colds Colds are very apt to cause asthma in allergic individuals

(f) A national campaign for education in and prevention of asthma and other allergic conditions is very necessary It should be highly successful because we can prevent or at least minimize symptoms in most cases

II Specific Treatment

Excellent results are usually obtained in those patients whose offending allergen or allergens have been removed In some, complete avoidance is impossible and hyposensitization is also necessary Both of these methods are highly important By elimination we avoid the specific allergens Hyposensitization is an attempt, usually successful, to raise the patient's resistance so that he can withstand *average* amounts of the offending allergen

(a) *Avoidance* If there were no exposure, there would be no attacks Complete avoidance leads to complete relief from symptoms i e, "cure" from a clinical point of view,—but this statement is only true in paroxysmal asthma Such elimination also is valuable in chronic asthma but complete relief should not be expected in patients who have already developed emphysema and chest deformities From an im

munologic point of view, "cure" is rare even in paroxysmal cases because recurrence usually follows re-exposure, e g, to a dog or cat

The patient is given written directions as to avoidance of offending foods and inhalants Care is emphasized and firmness is often necessary to actually see that the patient follows orders Many patients do not want to part with the family cat or dog, and others do not clean their homes from an allergic point of view If inhalation of house dust and/or feathers and kapok causes attacks of asthma the homes must be made as free from these allergens as possible Good vacuum cleaners with attachments are essential Rubber bedding or dust proof zippered covers are always ordered The bottoms of all soft furniture are boarded with linoleum so that dust cannot fall to the floor These are a few of the necessary measures

In allergy to foods the patient must completely avoid the particular food and all foods which contain it, e g, wheat and all wheat containing foods Halfway measures frequently fail Further details regarding elimination can be found in such textbooks as Bronchial Asthma by Unger

(b) *Hyposensitization* (desensitization) injections of increasing amounts of extracts of important allergens which cannot be avoided, e g, house and occupational dusts, pollens, fungi, animal danders, orris root, and cottonseed The results are usually good The oral method is occasionally used

The technic is described in Bronchial Asthma by Unger and many other books and articles It is relatively simple The beginning dilution is based on the degree of sensitivity of the patient to the particular allergen, e g, ragweed or horse dander The details vary with different allergists, but most men raise the dosages about twice a week until local reactions occur Great care is necessary to prevent constitutional reactions, as shown by asthma, rhinitis, urticaria and occasional shock The injections are usually necessary for a long time, but the intervals are lengthened to approximately every 2 4 weeks

III TREATMENT OF CONTRIBUTORY FACTORS

This consists chiefly of efforts to avoid those influences already discussed, e g, inhalation of various kinds of dusts, fumes, bacteria and viruses Psychogenic and endocrine factors must also be combatted, they rarely, if ever, initiate attacks of asthma, but they may aggravate or incite attacks in allergic persons who are also exposed to exciting allergens

IV SYMPTOMATIC TREATMENT

While non specific treatment is important, it gives less favorable and

less permanent results than can be secured from elimination of the specific factor, with or without hyposensitization This symptomatic treatment consists of measures used both during and between attacks

There are many available therapeutic measures but the author recommends the following

(a) Reassurance of the patient is the most important single measure The attacks may frighten the patient (and the family) Tell him that the attack will subside (and it almost always does) Death is rare in uncomplicated asthma (unless morphine has been used) The calm, confident attitude of the physician is very valuable to the patient Urbach was correct in saying that "the asthma doctor must and dare not forget that his own quiet, deliberate and reassuring manner and his absolute conviction that almost all cases of asthma can be cured, constitutes one of the most important prerequisites for success"

(b) Restrict the patient s activity The patient is already short of oxygen, needless exertion only aggravates

(c) The patient s room should be as dust free as possible, with bare floor or linoleum, dust proof bedding covers, clean curtains, and no animals If inhalation of pollen and/or fungi is a factor the windows must be shut or, better, an air filter should be installed in the window

Wesley Memorial Hospital (Chicago) has 12 beds especially designed to take care of severe asthmatic patients Filters clean the air and warm it in cold weather, the bedding is rubber, linoleum covers the floor, the furniture is steel and synthetic leather, and the rooms are practically dust free Almost every patient whose asthma is due to inhalation of an allergen is quickly relieved in such a room If his symptoms do not disappear in four to seven days he is probably allergic to a food or has some bacterial or other complication Every hospital should have similar rooms for allergic patients

(d) *Aminophyllin* is probably better than epinephrin except in children It does not excite the patient nor raise his blood pressure, nor does it cause tachycardia When given intravenously it acts quickly and usually gives prompt relief We recommend 0 24 gm (3¾ grains) given slowly with a 10cc syringe These injections can be repeated two to three times a day, if necessary If the patient is in a hospital the initial dose of 0 24 gm should be followed by 0 48 gm mixed with a liter of 5 per cent glucose at 60 drops per minute This liter mixture should be

given daily for three to four days, with subsequent relief in most cases. But, if symptoms persist, the needle should be left in the vein and the 'continuous method' should be used In this technique 1 0 to 1.5 gm aminophyllin are added to a liter of 5 per cent glucose, at 28 drops per minute (2 liters in 24 hours) The drip may be continued for as long as a week or more, if necessary, and the amount of aminophyllin is gradually reduced as symptoms subside This continuous method has been successful in many stubborn cases although it is not 100 per cent effective

Aminophyllin is also useful when given rectally (10 grains dissolved in 20cc tap water), or 7½ grain (0 50 gm) suppositories Aminophyllin by mouth is not very helpful and its intramuscular use is painful

(e) *Epinephrin* (1 1000) is best given in children (0 2 to 0 4 cc) It is also often excellent in adults in dosage of 0 50cc (larger amounts only make the patient 'nervous)

Epinephrin in oil (1 500) is injected intramuscularly once or twice daily The adult dose is 1 0cc , the child s 0 50cc Epinephr n 1 ... inhalation has almost entirely repl... En neph... v

a

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... exists A new slow acting epinephrine is now ..., it must be used cau vailable in the form of sus phrine dosage 0 10 to 0 40 cc

(f) *Ephedrin* in doses of ⅜ ½ grain (0 025 to 0 032 gm) orally useful in moderate and mild asthma It has epinephrin like effects, and should be combined with a sedative, e g , ephedrin and seconal Precautions are similar to those of epinephrin

(g) *Oxygen* inhalation is indicated in cyanosis or great weakness It is not of much avail in uncomplicated asthma Helium may be added but it is seldom used

(h) *Glucose* is a valuable food and perhaps has a more important role in asthma It is known that epinephrin forces glucose from the liver, hence patients who have received much epinephrin need glucose We therefore give each patient 5 ounces daily of glucose in a quart of fruit juices

(i) *Iodides* have stood the test of time. They act by loosening the sputum They may be combined with apomorphin, a good expectorant, as follows

Apomorphin hydrochloride	grains 2
Potassium iodide	drams 5
Syrup Cherry q s ad	ounces 4

Sig Teaspoonful four times daily

(j) *Syrup of ipecac*, teaspoonful every hour till emesis, is excellent in acute asthma, especially in children

(k) *Sedation* should be mild, e g , phenobarbital, or 50 mg benadryl

(l) An enema of 2 ounces of *ether* with 4 ounces of mineral oil is often helpful in severe cases A full ether anesthesia (30 to 40 minutes) may favorably terminate severe asthma

(m) *Morphine should never be used in bronchial asthma*, it is much too dangerous as it slows respiration and lessens the cough reflex and the expulsion of sputum We want the patients to expectorate the thick tenacious material which is usually responsible for symptoms (see Table III)

(n) The *diet* should be ample Patients who cannot eat much because of asthma should be encouraged to take small amounts at frequent intervals

(o) *Chemotherapy* is not indicated in uncomplicated asthma but antibiotics and/or sulfonamides should be given to those patients whose asthma is complicated by infection as shown by crepitant rales or areas of consolidation, and by leucocytosis, increased sedimentation rate and fever, chest x ray films may or may not help Penicillin is particularly valuable and should be given intramuscularly The newer oral antibiotics are also useful, e g , terramycin or aureomycin

(p) *Bronchoscopic* aspirations may be life saving, especially in patients who cannot expectorate sticky sputum Suffocation may occur if aspiration is too long delayed

(q) Last, but not least, let us discuss briefly the use of *ACTH* and *Cortisone* in severe asthma We have now used these two in a number of cases, the report of others, we can conclude In some cases of stat cus which have resisted the usual methods ent, these have given brilliant results We have used ore than In ospital we prefer to start by ut 20 m y to each liter of 5 per cent in mos 0 Gm aminophylline) The

patient receives 2 to 3 liters per 24 hours This technique works very well A more expensive way is to inject about 25 mg ACTH every six hours, with reduction in amount and increase in intervals if the patient improves After the patient's asthma has been relieved, the dosages of ACTH are gradually reduced, or one can substitute Cortisone by mouth, beginning with 25 mg, four times daily with smaller amounts as the patient continues to improve The treatment, either by ACTH or Cortisone, must be kept up for a long time as the asthma is very likely to recur when the hormone is stopped It is of course, necessary to use all due precautions ACTH and Cortisone should not constitute a substitute for a careful allergy survey

We may conclude by saying that by the judicious use of one or more of the above measures, the patient's attack can almost always be overcome Death is rare After the patient's attack has been relieved every effort should be made to prevent further attacks It is at this time that we should institute careful and thorough search for responsible allergens, with subsequent avoidance, and with hyposensitization to inhalant allergens, if necessary

(r) Space will not permit details as to *treatment of complications* of asthma. Suffice to say that the treatment must be directed both ways For example, an asthmatic patient who needs a cholecystectomy should first be placed in a dust free ("asthma") room When the asthma has subsided the operation should be carried out and the patient returned to the "asthma" room to prevent recurrence of asthma Lobectomy is definitely indicated in most asthmatic patients who also have bronchiectasis provided the bronchiectasis is not too extensive and the patient is a good risk

Results of Treatment in Bronchial Asthma

Results in paroxysmal asthma are usually brilliant if the above care and precautions are observed This especially applies to those patients who have had a careful history and examination and who have also had complete skin tests and laboratory studies,—all this followed by avoidance of offending allergens, with or without specific hyposensitization

In chronic asthma however complete relief from symptoms is uncommon because of irreversible changes, e g, emphysema

The results are therefore much better in children as shown in Tables VI and VII

TABLE VI

RESULTS OF TREATMENT IN 459 CASES OF BRONCHIAL ASTHMA

Age at Onset	Paroxysmal 100% Cured	Paroxysmal Improved	Paroxysmal Unimproved	Paroxysmal Dead	Chronic 100% Cured	Chronic Improved	Chronic Unimproved	Chronic Dead
0–9	55	81	5	3	–	23	9	5
10–19	9	29	6	–	2	13	9	4
20–29	17	27	4	2	–	8	10	4
30–39	8	17	5	1	–	11	7	6
40–49	4	17	–	3	2	7	9	11
50–59	–	2	1	2	–	9	4	4
60–69	–	–	–	–	–	1	–	3
TOTALS	93	173	21	11	4	72	48	37

TABLE VII

SUMMARY OF RESULTS OF THERAPY IN 459 CASES OF BRONCHIAL ASTHMA

	100% (Cured)	Improved	Unimproved	Dead	Total
Paroxysmal	93 (31 2%)	173 (58 0%)	21	11	298
Chronic	4 (2 4%)	72 (44 7%)	48	37	161
TOTAL	97	245	69	48	459

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CHAPTER XI

EMPHYSEMA OF THE LUNGS

By Ronald V Christie, M D

PULMONARY emphysema may be defined as a condition in which the alveoli of the lungs are dilated and their walls overdistended When used in this wide sense the term includes four clinical entities — chronic obstructive or hypertrophic emphysema, senile, postural or atrophic emphysema, acute vesicular emphysema, and localized or compensatory emphysema

CHRONIC OBSTRUCTIVE EMPHYSEMA

(*Synonyms* Hypertrophic emphysema, chronic vesicular emphysema)

This is the most common form of emphysema and is the type referred to when a diagnosis of "emphysema of the lungs" is made

Aetiology

Numerous hypotheses have been advanced to explain the cause of this type of emphysema, but most are based only on conjecture and are incapable of experimental proof or analysis Certain facts, however, stand out clearly almost all patients suffering from this disease are men of middle age or over who give clear evidence of chronic respiratory obstruction due to asthma, or chronic bronchitis, or to persistent coughing from pulmonary tuberculosis, bronchiectasis, or pneumokoniosis It has also been shown experimentally that tracheal or bronchial obstruction, if sufficiently pronounced and prolonged, usually leads to emphysema This correlation between respiratory obstruction and emphysema cannot be denied, but the mechanism by which obstruction leads to the changes characteristic of emphysema is in considerable dispute, and numerous theories have been advanced The "expiratory" theory supposes that the air sacs become overdistended because, owing to expiratory obstruction, they cannot properly be emptied The "inspiratory" theory claims that overdistension is produced because too much air is drawn into the lungs by the increased inspiratory effort associated with coughing and respira-

tory obstruction There is also a theory that the primary cause is increased stress and strain on the walls of the alveoli On coughing the pressure of air in the alveoli may rise to 50 mm of Hg or more, and in asthma a comparable pressure change may occur It is suggested that the stress and strain of these pressure changes will in time destroy the elasticity of the alveolar wall in much the same way as the chronic stress of hypertension will destroy the elasticity of the arteries The evidence

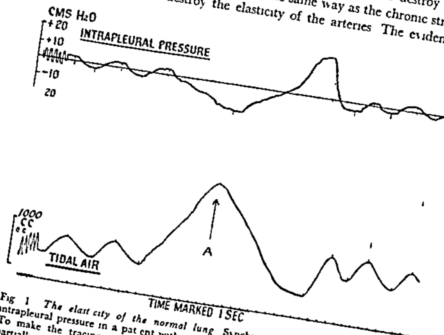


Fig 1 *The elasticity of the normal lung* Synchronous tracing of tidal air and intrapleural pressure in a patient with a minimal tuberculosis lesion at the right apex To make the tracing comparable with that shown in Fig 2 the lung has been partially collapsed by a pneumothorax so that the pleural pressure fluctuates around that of the atmosphere At A a deep breath is taken maximal distension of the lung corresponds closely to the time when the intrapleural pressure is most negative The elasticity of the lung is intact (From Christie & McIntosh *J Clin Investigation* 13 291 1934)

that loss of elasticity in the lungs may lead to the changes observed in emphysema is given in section on Functional Pathology

It has also been suggested that the degenerative changes in the lung are primary, or that they are secondary to changes in the thoracic cage, but the evidence given is unconvincing to say the least The theories that best fit the established aetiological factors in this disease are the "expiratory" theory and the theory that the primary lesion is loss of elasticity

from the stress and strain of coughing or respiratory obstruction It is probable that both may play a part in producing emphysema

Heredity has been emphasised as a factor, but it seems more probable that any hereditary tendency is towards conditions such as asthma which may lead to emphysema

The statement that glass blowing or the playing of wind instruments may lead to emphysema survives from the text books of last century, although there is ample published evidence that no such aetiological relationship exists

Pathology

There is a characteristic increase in the antero posterior diameter of the thoracic cage, the so called "barrel shaped chest" There is usually a moderate degree of kyphosis involving all the thoracic vertebrae, and the vertebral cartilage may be thin and compressed anteriorly The ribs are widely spaced and run horizontally and their cartilages are frequently calcified

The pleura is thin, pale, and flimsy, and adhesions are common The lungs are voluminous and do not collapse when the thorax is opened which is proof that the elastic recoil of the lung is lost The surface may present a corrugated effect, the result of rib indentation, and bullae due to the protrusion of greatly distended alveoli are frequently seen The lungs are dry and light, but pit on pressure not because they are oedematous, but because they have lost their elasticity On section many of the alveoli can be seen to be dilated and their walls are thin and in places ruptured so that differentiation of the lobules into alveoli, atria and alveolar ducts may be impossible The capillaries appear to be narrowed and may be torn and obliterated These changes are usually most marked at the apices and along the margins of the lung Sclerosis of the pulmonary arterioles may be conspicuous The bronchioles and alveolar ducts are dilated and the sudden transition from alveolar duct to atrium is lost The larger bronchioles and bronchi may be dilated in a fusiform manner but this change is seldom sufficiently pronounced to be confused with bronchiectasis There is usually evidence of chronic bronchitis In advanced cases there may be evidence of ' cor pulmonale and right heart failure and often there is hypertrophy of the left ventricle, the cause of which is unknown

Clinical Picture

The cardinal symptom of emphysema is breathlessness on exertion, and although this does not appear until the disease is well established it

is unwise, in the absence of dyspnoea to make a definite diagnosis of emphysema of the lungs Over a period of months or years the patient complains of increasing breathlessness on exertion but any improvement *in cough or bronchospasm may be accompanied by a diminution* in the dyspnoea For this reason patients often state that they are better during the summer months In emphysema the diagnostic importance of dyspnoea is considerable and experience has shown that if a middle aged patient with a previous history of chronic cough or asthma develops breathlessness on exertion which cannot be accounted for by cardiovascular disease or bronchospasm the probability that he has emphysema should always be considered It should not be forgotten however, that those with chronic bronchitis not infrequently develop bronchospasm after exercise, this cause of dyspnoea is usually suggested by the history and can often be established by examining the chest for evidence of bronchospasm after exertion sufficient to produce mild dyspnoea

Cyanosis is often inconspicuous even in patients who are very dyspnoeic, but may be severe particularly in the terminal stages of the disease when there may be secondary polycythaemia The primary cause of this cyanosis is inability to aerate the blood but peripheral stasis and polycythaemia may also be important factors

The progress of the disease is usually slow and insidious, but rarely it is rapid and the patient may be incapacitated within a year or two of the onset Commonly there is a slow progression of symptoms over many years and if the patient does not die of intercurrent infection the symptoms and signs of right sided heart failure and cor pulmonale supervene Spontaneous pneumothorax from rupture of a bulla may occur, less frequent complications are haemoptysis and interstitial emphysema Failure of vision due to papilloedema is a very rare complication, but has been described in those patients with secondary polycythaemia

Physical Signs

The thorax is large and barrel shaped, the greatest increase being in the antro-posterior diameter This is due partly to the inspiratory position of the chest and partly to dorsal kyphosis usually involving all the thoracic vertebrae The intercostal spaces are wide and the ribs tend to run horizontally so that the subcostal angle is increased The supra clavicular hollows are often filled and the neck appears to be short Expansion of the chest on inspiration is limited and is replaced by a general elevation of the thorax heaving in character Expiration is visibly prolonged The

apical impulse is seldom visible, but in contrast epigastric pulsation is often marked, presumably due to the low position of the diaphragm. On palpation the vocal fremitus may be unaltered or diminished. The apical impulse can seldom be felt.

On percussion the note is hyperresonant, often more so than in pneumothorax and the degree of hyperresonance may vary in different areas. The cardiac dullness is masked and the limits of lung resonance at the bases are increased because the diaphragm is low.

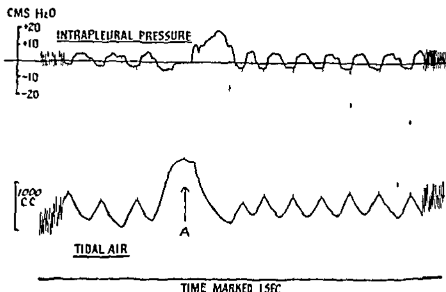


Fig. 2. *The elasticity of the emphysematous lung.* Synchronous tracing of tidal air and a pneumothorax of 40 cc. on the right side. The pleural pressure fluctuates around that of the atmosphere. At A, when a deep breath is taken, the pleural pressure becomes only slightly more negative and at the end of inspiration it returns to that of the atmosphere. The lung does not start to deflate until the pressure becomes positive. These changes indicate that the elasticity of the lung has been lost. (From Christie, *J. Clin. Investigation, 13* 300, 1934.)

On auscultation the breath sounds are usually faint, particularly at the bases, but may be increased in intensity by the concomitant bronchitis or bronchospasm, when coarse or sibilant rhonchi may be heard. The duration of expiration is prolonged. Vocal resonance is usually diminished. The heart sounds are faint.

Although the description of the physical signs of emphysema in most text books of Medicine is precise and dogmatic, comparisons of clinical and postmortem findings have clearly shown that a diagnosis based on physical signs alone may be entirely fallacious. Many of the physical signs

of emphysema such as the large chest with diminished expansion, obliteration of the cardiac dullness and absence of the apical impulse, can be found in men of middle age or over, and it has been clearly shown that these signs are not in themselves indications of emphysema they may only reflect the fixation of the thoracic cage which is one of the degenerative changes which may occur after middle age For this reason the diagnosis of emphysema should be reserved for those who have the symptoms as well as the physical signs of the disease

X-ray

The radiographic appearances in emphysema are characteristic, but may be absent even in the advanced stages of the disease The intercostal spaces are wide and the ribs horizontal The diaphragm is low, its outline often irregular and its movement limited The translucency of the lung fields is increased, especially at the bases and there is usually an *increased hilar shadow* Rarely *bullae are seen as annular shadows* which occasionally resemble tuberculous cavitation The heart is pulled down by the diaphragm and may be narrow and spindle shaped Injection of iodized oil may show fusiform dilatation and sometimes "beading" of the bronchi

Vital Capacity and Lung Volume

The vital capacity is reduced but not always in proportion to the severity of the disease More significant is an increase in the residual air or functional residual air, but this measurement is a complicated procedure and is not within the scope of routine clinical investigation

Functional Pathology

Almost all the physical signs of emphysema can be explained by the loss of elastic recoil, or elasticity of the lung, which occurs in this disease In health the elastic recoil of the lung towards the hilus is counterbalanced by traction of the chest wall and diaphragm If the traction of the thoracic cage is abolished, as happens when the thorax is opened on the post mortem table, the lungs collapse towards the hilus, and conversely if the elastic recoil of the lung is abolished, as happens in emphysema, the thoracic cage will tend to assume the inspiratory position With the thoracic cage already in the inspiratory position before inspiration commences, the patient with emphysema must use the accessory muscles to draw air into the lungs, hence the heaving type of inspiration seen in this disease The patient with emphysema will

encounter even greater difficulty in expelling air from his lungs Normally expiration is largely, if not wholly, a passive act *the thoracic cage* is pulled inwards by the elastic recoil of the lung When this recoil is lost, as in emphysema, the lung has to be squeezed to be deflated The respiratory musculature was not built for this task, and the intercostals have to be assisted by the accessory muscles of expiration Expiration becomes an active muscular act, and is prolonged as it is in other conditions, such as asthma and tracheal obstruction, in which the lungs have to be compressed to be deflated

Loss of elasticity could also explain the over distension of air sacs, with formation of bullae on the surface of the lung With loss of elasticity the expanding force is no longer equally distributed, and equal expansion in different parts of the lung should not be expected In fact, the greatest expansion should occur where the force is applied which is at the surface of the lung With each inspiration one would *expect the superficial air sacs to be strained and stretched to a greater* extent than the air sacs deep in the lung, and with this process going on for months and years, it is easy to understand the formation of bullae on the surface of the organ

The effect of these changes on the efficiency of pulmonary ventilation is probably considerable On theoretical grounds at least, one might expect that these superficial and relatively functionless over distended air sacs should be over ventilated at the expense of the more normal alveoli which lie deep in the lung This abnormal distribution of ventilation could explain the impairment of hæmo respiratory exchange and the established fact that the mixing of gases in the emphysematous lung is not homogeneous as it is in the normal

Loss of elasticity may also affect the circulation Normally there is a negative pressure within the thorax which facilitates the return flow of venous blood to the heart In emphysema this negative pressure is abolished because, owing to loss of elasticity the structures within the thorax are no longer "on the stretch" During expiration the intra *thoracic pressure may in fact become positive this will impede the* return flow of blood and is in part responsible for the elevation of the venous pressure which frequently occurs

The cause of dyspnœa on exertion in emphysema is almost certainly inability to eliminate the excess of carbon dioxide suddenly produced by muscular effort this leads to an uncompensated gaseous acidosis, and dyspnœa is *inevitable* Under resting conditions dyspnœa does not occur

since even if the lungs cannot maintain gaseous equilibrium, the kidneys have ample time to compensate for almost any degree of CO_2 retention the CO_2 combining power may increase leading to a compensated

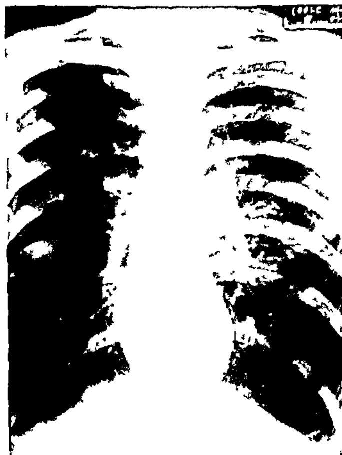


Fig 3 X ray of the chest in a case of chronic obstructive emphysema. The intercostal spaces are wide and there is increased translucency of the lung fields especially at the bases The hilar shadow is prominent and the heart long and narrow The diaphragm is low and irregular in outline

gaseous acidosis with as might be expected no resting dyspnoea Several factors contribute towards the impairment of CO_2 elimination Unequal ventilation of the lung is probably the most important much of the inspired air being wasted in ventilating the superficial alveoli many of which are overstretched avascular and relatively functionless The in

ability of the patient to increase pulmonary ventilation must also be a factor since even the power of voluntary hyperventilation is often greatly diminished

Treatment

The treatment of emphysema is essentially symptomatic as elastic tissue cannot regenerate and nothing can restore the structure of the lungs The treatment of asthma or chronic bronchitis, if present is of course very important Any factor which induces cough should be avoided or eradicated, and numerous expectorant and sedative cough mixtures have been recommended Exercise, sufficient to produce dyspnoea should if possible be avoided

Although there may be no evidence of bronchospasm or resistance to respiration the administration of bronchodilator drugs such as ephedrin not infrequently relieves the dyspnoea of emphysema, particularly if the patient can tolerate large doses A possible explanation, supported by the pathological changes which can be observed in the lung is that the bronchioles leading to the over-distended air sacs and bullæ are less capable of changes in calibre than those leading to healthier parts of the lungs, bronchospasm, although not clinically manifest, would in this case increase the proportion of the inspired air deflected to these useless parts of the lung, the relief of bronchospasm with ephedrin would improve the efficiency of ventilation and thus relieve dyspnœa

Several procedures, the purpose of which is to deflate the lung, have been described, and it is said that these increase the efficiency of respiration Pneumothorax is one, and relief of dyspnœa both in man and in horses suffering from this disease, has been claimed, but this procedure is dangerous owing to risk of rupture of the flimsy visceral pleura More popular and less dangerous are respiratory exercises designed to teach the patient to deflate the lung and to increase the use of the diaphragm A well fitting abdominal belt will also raise the diaphragm by increasing intra abdominal pressure, and recently pneumoperitoneum has been suggested for the same purpose All these procedures have been recommended, and various theories have been put forward to explain the beneficial effects observed Two effects are common to most of them First, the diaphragm is raised so that its convexity is increased and its efficiency therefore enhanced Secondly, the lung is deflated by these procedures so that it contains less air The decrease in volume is, however, very small — so small that it can hardly be measured — and the beneficial effects are probably for the most part due to increased effi

ciency of the respiratory musculature It is also possible that with greater collapse of the superficial bullæ efficiency of ventilation may be increased

When emphysema is complicated by bronchopneumonia or heart failure oxygen should be given, as the added insult of anoxia to a heart that is failing for other reasons, greatly lessens the chances of recovery

The treatment of emphysema is thus far from being hopeless although it is essentially symptomatic Bronchodilator drugs should be tried in all cases Respiratory exercises or an abdominal belt, or both, may increase considerably the tolerance to exercise And lastly, when heart failure or bronchopneumonia supervenes oxygen therapy is of the greatest value

SENILE EMPHYSEMA

(*Synonyms* Atrophic emphysema Postural emphysema)

As its name implies this is essentially a disease of old age The chest is usually barrel shaped but there is usually no significant enlargement of the thoracic cage The deformity is probably due largely to atrophy of the intervertebral discs leading to kyphosis, with consequent rotation of the ribs so that the sternum is pushed forward and the chest becomes barrel-shaped The kyphosis is usually upper dorsal but the whole thoracic spine is stiff

The lungs may be normal in size or they may be small, and the same changes may be found in them as in the obstructive type of emphysema, but these are seldom severe Unless there is an associated chronic bronchitis, in which case the picture will be complicated by the obstructive element, symptoms are seldom conspicuous With severe kyphosis there may be heart failure but this is more likely to be due to the spinal deformity than to be a sequel of emphysema

ACUTE VESICULAR EMPHYSEMA

In acute respiratory infections, acute bronchial asthma, diphtheria or any condition associated with severe respiratory obstruction, the lungs may become overdistended Only if attacks are recurrent is there any danger of the development of chronic emphysema, children in particular are remarkably tolerant to repeated attacks of respiratory obstruction

LOCALIZED EMPHYSEMA

(*Synonym* Compensatory emphysema)

This patchy or localized form of emphysema may be associated with a 'ball valve' obstruction to part of the lung which permits the entry

of air, but does not allow its exit, or with collapse or contraction of portions of the lung. In the neighborhood of bronchopneumonic or fibrotic patches, or of a lobe collapsed by occlusion of its bronchus, dilatation and overdistension of alveoli may occur, since if one part of the lung shrinks the adjacent lung must either expand or the chest wall be drawn in If the contraction is sufficient to displace the mediastinum, the contra-lateral lung may also be overdistended

CHAPTER XII

FOREIGN BODIES IN THE AIR AND FOOD PASSAGES

By Chevalier L Jackson M D

Though the primary concern of this book is with diseases of the bronchi and lungs, in dealing with foreign bodies it is necessary to consider also foreign bodies in the esophagus, because of the close interrelationship in symptomatology, diagnosis and treatment

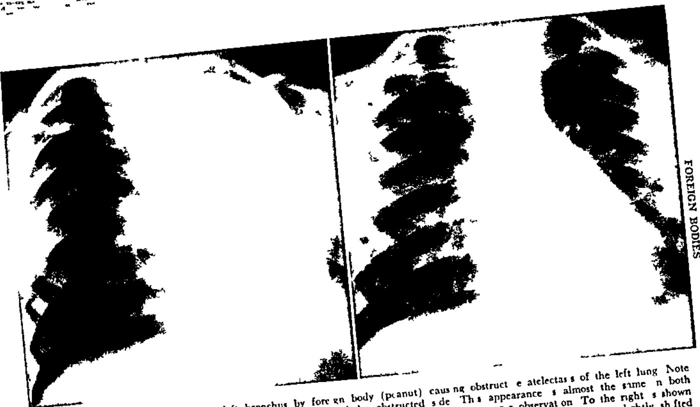
The study of foreign bodies in the bronchi and lungs is important to the chest physician not only in order to be able to deal intelligently with cases of foreign body encountered in clinical practice, but also in order to understand modern bronchology Our present knowledge of the mechanism of physical signs is due almost entirely to foreign body experience. The recognition of the true nature of postoperative atelectasis was definitely a consequence of the familiarity with bronchial obstruction acquired in dealing with foreign bodies The roentgen signs of bronchial obstruction and the roentgen diagnosis of obstructive emphysema and obstructive atelectasis were learned from the roentgenologist's experience in cases of peanut kernels, beans and other nonopaque foreign bodies lodged in the bronchi (Fig 1) Of course, his understanding of these cases was in turn dependent upon earlier experience with opaque foreign bodies

Etiology

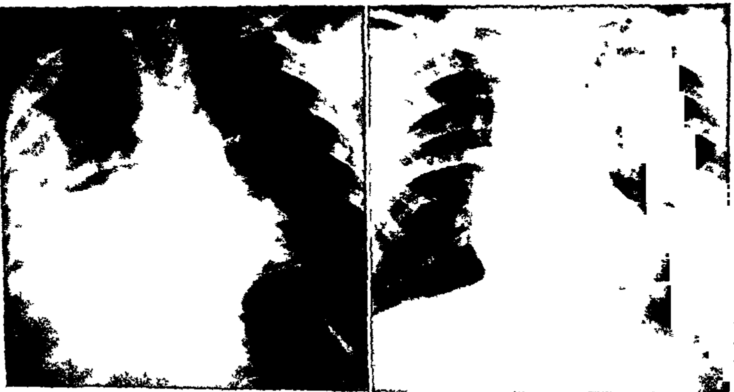
Personal factors such as age, sex, occupation, social conditions and place of residence are, of course, of significance in the etiology of foreign body For example, 79 per cent of the cases of peanut as foreign body occur in children Failure of natural protective mechanisms can also be considered an etiologic factor Many foreign bodies are inhaled or swallowed during sleep, alcoholic intoxication, epilepsy, or some other form of unconsciousness Physical factors such as emotional reactions, activities and posture may play a part In a certain small percentage of cases,



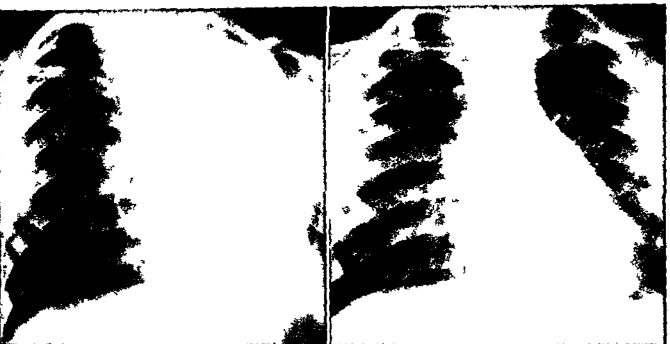
Fig 1 *Above*, obstructive empysema of the right lung due to partial (check valve) obstruction of the right bronchus caused by a non opaque foreign body (peanut) Note that in the inspiration film at the left, it is difficult to detect *any difference* in the aeration of the *two lungs* and the heart is in normal position while in the expiration film at the right the right lung is obviously "ballooned" the diaphragm flattened and the heart and mediastinal structures shifted to the opposite side



Below con plete obs ru t on of the l ft bronchus by fore gn body (peanut) caus ng obstruct e atelectas s of the left lung Note that the heart and med ast nal structures rema n sh fted toward the obstructed s de Th s appearance s almost the same n both exp ra ory and nsp ratory phases there s l ttle med ast nal sh ft noted even on fluoroscop c observat on To the right s shown the appearance after reaerat on of the l ft lung follow ng removal of the fo e gn body The heart remains very sl ghtly sh fted toward tl e left but the lung s almost completely reaerated



F g 1 *Above* obstruct e empysema of the right lung due to par al (check val e) obstruct on of the right bronchus caused by a non opaque fore gn body (peanut) Note that n the nsp ration film at the left t is d fficult to detect any d fference n the aerat on of the two lungs and the heart s n normal pos on wh le n the exp rat on film at he r ght the r ght lung s obv ou ly ballooned the d aphragm flattened and the heart and med as nal structures sh fted to the oppos e s de



Below complete *obstruct* on of the left bronchus by *fore gn* body (peanut) caus ng obstruct e *atelectas s of* the left lung Note that *the heart* and med ast nal structures rema n *sh fted toward* the obstructed s de Th s appearance s almost the same in both exp *ratory* and nsp ratory phases there s *l ttle med ast nal sh ft* noted e en on fluoroscop c *observat on* To the right s shown the appearance after reaerat on of the left *lung follow ng* remo al of the fore gn body *The heart* remains very sl ghtly sh fted toward the left but the lung s almost *completely reaerated*

dental and surgical accidents may be the cause of lodgement of a foreign body Properties of the foreign body itself may constitute a cause However, an exhaustive study of this subject by Chevalier Jackson showed that carelessness of one kind or another was the most important etiologic factor Carelessness in placing inedible substances in the mouth carelessness in the preparation of food, carelessness in hasty eating, carelessness in allowing children to play with small objects which might be considered potential foreign bodies, carelessness in giving peanut candy to infants without molars—all of these forms of carelessness have been shown to be causes of foreign body accidents

Pathology

The pathologic changes produced by foreign body in a bronchus are due in part to the nature of the foreign body, but more often depend upon the degree of bronchial obstruction produced Smooth metallic and nonobstructive foreign bodies cause little if any, pathologic reaction On the other hand a metallic foreign body that is rough or obstructive will cause marked reaction In a case of vegetable foreign body the degree of reaction will depend not only on degree of obstruction, but also on the irritating character of the foreign body itself It has long been recognized that peanuts, for example produce a violent inflammatory reaction in the bronchial mucous membrane especially pronounced in children This has been called "arachidic" or "vegetal" bronchitis

Bronchial obstruction, regardless of the nature of the foreign body causes varying degrees of bronchopulmonary suppuration Purulent bronchitis, bronchiectasis, pulmonary abscess and empyema can all result from bronchial obstruction due to foreign body (Fig 2) Though these complications may prove very grave, and may require surgery Chevalier Jackson pointed out that suppuration of foreign body origin is definitely more amenable to treatment, and of more favorable prognosis than suppuration of other origin

Thus far we have been speaking principally of what might be called exogenous foreign bodies that is objects not only foreign to the air and food passages but originating from outside the body We should also consider foreign bodies of endogenous origin, because their symptomatology, diagnosis, pathology and treatment are similar Among such endogenous foreign bodies might be mentioned crusts of secretions crusts of clotted blood, broncholiths, sequestra, fragments of lymphnodes and sloughs of any kind Broncholiths are among the most commonly

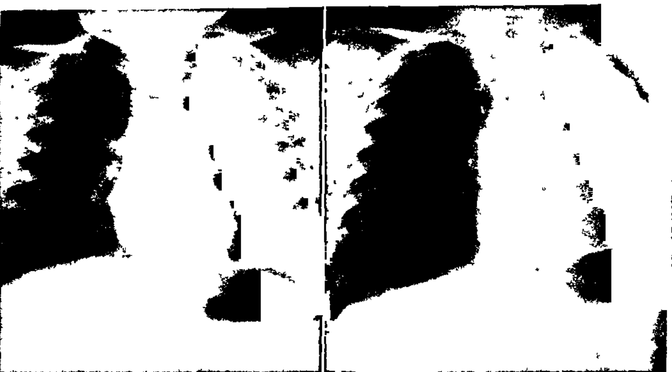


Fig 2 Empyema due to obstruction of right bronchus by foreign body of long sojourn (one year) This tack was easily removed by bronchoscopy, but of course, simultaneous surgical drainage of the empyema was required To the right is shown the final result with restoration of the lung to normal condition Bronchial obstruction must always be thought of as an etiologic and perpetuating factor in empyema.

recognized endogenous foreign bodies (Fig 3) They consist of calcific and phosphatic material, either originating in a lymphnode or forming in the bronchial lumen The bronchial casts occurring in fibrinous bronchitis, diphtheria and some other conditions are also common as endogenous foreign bodies

Foreign bodies in the esophagus cause slight if any pathologic changes unless they remain for a long time Eventually erosion of the esophageal wall occurs as a result of pressure, periesophageal inflammation develops, and sometimes this may extend to the pleura or into a bronchus Cases have been reported in which suppuration continued until a fistula discharging externally was established Of course, cicatricial stricture very often develops at the site of lodgement of a foreign body if the foreign body is not removed within a reasonable time It is surprising, however, what slight changes may occur even in a case of very long sojourn (Fig 4)

Symptomatology and Diagnosis of Foreign Body in the Air and Food Passages

According to Jackson and Jackson, "initial symptoms are choking gagging, coughing and wheezing often followed by a symptomless interval The foreign body may be in the larynx, trachea, bronchi, nasal chambers, nasopharynx, fauces, tonsils, pharynx, hypopharynx, esophagus, stomach, intestinal canal, or it may have been passed by bowel or coughed out, or spat out, with or without the knowledge of the patient The initial symptoms may have escaped notice or may have been forgotten by the time the physician is consulted When a child has been known to choke, gag or cough while suspected of having something in his mouth, the case should be regarded as suspicious of foreign body until foreign body is excluded by appropriate diagnostic means Cyanosis is not uncommon and asphyxia may terminate the case in the initial stage Pain is not felt in the bronchi, and rarely in the trachea, though it may be felt in the case of esophageal foreign body, at each swallowing act

The differential diagnosis as to location of the foreign body is of the greatest importance Let us consider the differential diagnosis between foreign body in the larynx trachea, bronchi and esophagus In the case of *laryngeal* lodgement one or more of the following laryngeal symptoms may be present hoarseness, croupy cough, aphonia, hemoptysis, wheezing, dyspnea, cyanosis As stated above, obstructive foreign body may be quickly fatal by laryngeal impaction, but the lodgement



Fig 3A Empyema on the right side

of a nonobstructive foreign body in the larynx may be followed by an almost symptomless interval Mirror laryngoscopy in adults or direct laryngoscopy in children is necessary for diagnosis, though roentgen ray examination is also helpful It must be borne in mind that laryngeal symptoms may persist from the trauma of a foreign body that has passed into the deeper air or food passages or one that has been coughed out On the other hand laryngeal symptoms may be due to digital or instrumental efforts at removal of a foreign body, whether or not any was present It should also be remembered that foreign body in the hypopharynx or cervical esophagus can cause laryngeal symptoms

Tracheal foreign body is diagnosed by typical signs which have been described as the *audible slap* and *palpatory thud,* and *asthmatoid*



Fig 38 Lateral roentgenogram showing empyema on the right side

wheeze These signs first described by Chevalier Jackson are considered pathognomonic Cough dyspnea and cyanosis may be present The diagnosis is made by the elicitation of the above signs and the roentgen ray The palpatory thud is felt by placing the finger on the thyroid cartilage (Adam s apple) and asking the patient to cough At the same time the audible slap is heard at the open mouth The asthmatoid wheeze is likewise heard at the patient s open mouth It is characteristic of tracheal foreign body to move about in the trachea rather than remaining in one place as foreign bodies in the larynx, bronchi and esophagus generally do

In a case of *bronchial* foreign body the initial symptoms are as described above coughing choking a wheeze, etc There may be a history of foreign body inhalation or a suggestive history of a foreign ob



Fig 30 Bronchogram portrays bronchiectasis in right lower lobe and shrinkage of middle lobe after drainage of empyema

ject in the mouth Not infrequently a symptomless interval will follow, but before long cough recurs In a case of nonobstructive metallic foreign body symptoms may not recur for weeks or months, but in the case of an even slightly obstructive object a wheeze is noted, and if this sign is present it constitutes one of the most definite signs of foreign body Vegetable foreign bodies such as peanut kernels, beans, watermelon seeds, and so forth, cause a violent laryngotracheobronchitis with cough and irregular fever Bones animal shells and inorganic bodies may also produce chills, fever and suppuration but only after a longer period (Fig 5)



Fig 3D Specimen of the carnified and bronchiectatic right lower lobe resected by lobectomy Insert shows the broncholith which caused bronchial obstruction bronch ectasis and empyema

The diagnosis of bronchial obstruction by physical signs and roent gen-ray examination must be perfectly understood by the chest physician For proper understanding of this subject it is only necessary to recognize the fact that there are three fundamental types of valvular obstruction which have been called the *by-pass valve*, the *check-valve* and the *stop-valve* types (Fig 6) When first degree or by-pass valve obstruction is present, air passes in both directions with only slight interference, and a wheeze is produced, but very sligh or roentgen ray signs are

noted When the obstruction is just a little greater, so that air passes on inspiration but is trapped on expiration, a check valve type of obstruction is present and *obstructive* emphysema is produced, while if the valvular obstruction is complete, or of the stop valve type, no air passes in either direction, but the air in the distal portion of the lung is soon absorbed and *obstructive atelectasis* results The most characteristic phy



Fig 4 Roentgenogram showing nonopaque foreign body (wooden button) lodged in the esophagus of a young woman for 20 years This foreign body was easily removed and the cicatricial stricture which had been produced was successfully dilated by esophagoscopy

sical signs of bronchial obstruction are limited expansion decreased vocal fremitus, impaired percussion note, diminished intensity of breath sounds distal to the foreign body and absence of vocal resonance and vocal fremitus These last signs are noted in cases of complete obstruction and may lead to an erroneous diagnosis of empyema, whereas only obstructive atelectasis is present

The diagnosis of obstructive emphysema is quite easily made by fluoroscopy It is noted that the mediastinal structures shift away from

the obstructed side on expiration, while the obstructed side remains ballooned and the diaphragm remains flattened on that side, though rising normally on the unobstructed side In order to make a good film record of obstructive emphysema it is necessary to take one film on full inspiration and one on full expiration Very often the film taken on inspiration will appear grossly normal but the film taken at the end of expiration will clearly demonstrate the emphysema (Fig 1)

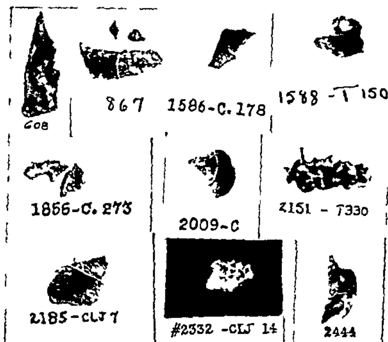


Fig 5 Specimens of bones occurring as overlooked foreign body in the lung (sojourn 6 weeks to ten years) These specimens may be seen at the Mutter Museum of the College in Philadelphia. The bones include beef veal chicken and squirrel bones and one fragment of a patient's own turbinate

In obstructive atelectasis the mediastinal structures remain over toward the obstructed side in both phases of respiration and the diaphragm on the obstructed side remains high Again, for film record it is best to take a film on full inspiration and one on full expiration The diagnosis of the exact site of lodgement of a foreign body should be made according to not only lobar but segmental localization, whenever possible (Fig 7)

Esophageal foreign body is diagnosed by the history, subjective sensation of foreign body and roentgen ray examination In most cases, there

is some subjective sensation of foreign body and occasionally pain As already mentioned symptoms referable to the air passages may be produced by foreign body in the esophagus as the result of compression of the air passages or overflow of secretions or in cases of long sojourn erosion of the foreign body through the party wall into the trachea or bronchus Such symptoms may also have been produced by digital or instrumental efforts at removal of a foreign body Preexisting esophageal disease must always be considered when a foreign body lodges (Fig 8)

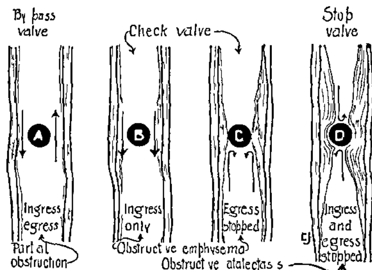


Fig 6 Simple schemas showing mechanism of the three common types of valvular bronchial obstruction by pass valve check valve and stop valve which produce a wheeze obstruction emphysema and obstructive atelectasis respectively

This is one reason for routine postoperative roentgen ray examination The roentgen ray will show clearly the presence and the location of opaque objects but in the case of non opaque objects such as many kinds of buttons (Fig 9) and some bones it will be necessary to administer an opaque mixture As a matter of fact a properly taken lateral film of the neck with the shoulders well down and the chin up will almost invariably show even a very small bone without the use of an opaque mixture (Fig 10) The great majority of foreign bodies in the esophagus are found in the cervical region between the esophageal introitus and the superior thoracic aperture unless there is some preexisting obstruction present.

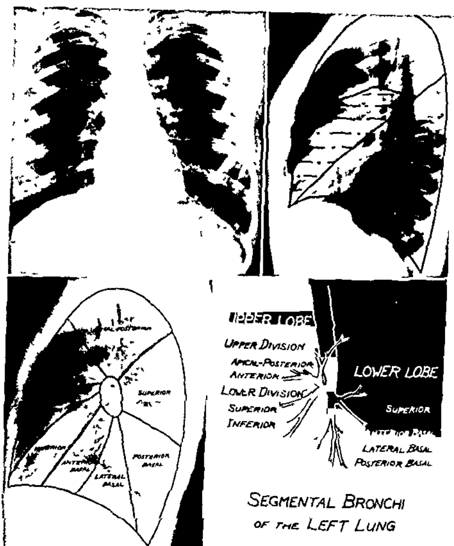


Fig 7 Case of foreign body demonstrating the importance of lobar and segmental localization by means of the combined study of roentgenograms in the posterior and lateral projections This foreign body, which appears from the anteroposterior film to be in the left main bronchus is found on study of the lateral projection to be in the superior segmental branch of the lower or lingular division of the left upper lobe bronchus Such localization is obviously very important in all bronchoscopic procedures (Below is shown bronchogram and key with names of segments of left lung and corresponding segmental branch)

Prognosis

Prognosis of foreign body in the air and food passages is excellent, provided prompt diagnosis is made, and skillful removal accomplished Before the present development of peroral endoscopy, foreign body entailed a high mortality rate, and even now foreign bodies that are not promptly diagnosed and removed are certain to cause serious illness sooner or later, and may prove fatal

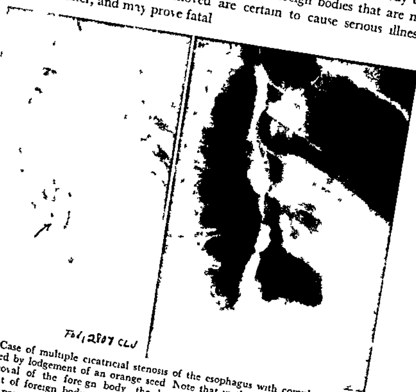


Fig 8 Case of multiple cicatricial stenosis of the esophagus with complete obstruction caused by lodgement of an orange seed Note that in the film to the right taken after removal of the foreign body the lowermost stricture is well demonstrated Lodgement of foreign body in the thoracic esophagus of the adult is nearly always due to the preexistence of some sort of stenosis

Treatment

Foreign bodies in the air and food passages can almost always be removed by peroral endoscopy, with the exception of foreign bodies in the intestines, below the duodenum When confronted with a case of foreign body in the larynx, trachea, bronchi, esophagus or stomach, the peroral endoscopist should study films made in both anteroposterior and lateral projections and perhaps some additional ones, and he should

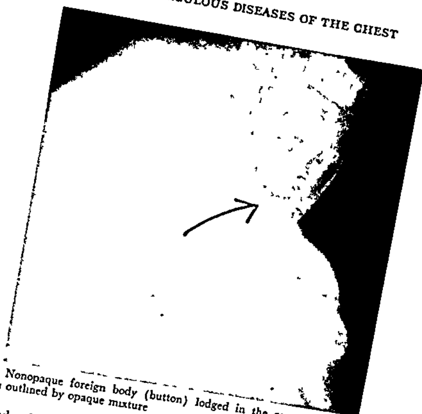


Fig 9 Nonopaque foreign body (button) lodged in the cervical esophagus, well shown as outlined by opaque mixture

then study the foreign body itself, using if possible a duplicate of the object, secured from the patient or parents of the patient. Always, the mechanical problem should be studied before the endoscopic procedure for removal is begun This study of the problem and the selection of the best types of forceps for the particular case contribute largely to success Presentation of the object should be studied just as presentation of the foetus is studied by the obstetrician before attempt at delivery. The relation of position of the visible parts of a foreign body and the probable position of the unseen portions are taken into consideration In many cases version or some other manipulation is required to convert an unfavorable into a favorable presentation. In the case of pins, a search is made not for the foreign body alone, but for its point. Pins and other small objects lodged in peripheral bronchi can be removed only by bronchoscopy under fluoroscopic guidance (Fig 11). Space does not permit a detailed discussion of the mechanical problems presented by different kinds of foreign body, but this subject has been fully discussed in works devoted to the subject, which are available for reference.

Fig 10 Thin bone in the cervical esophagus clearly demonstrated by roentgen film without the use of opaque mixture

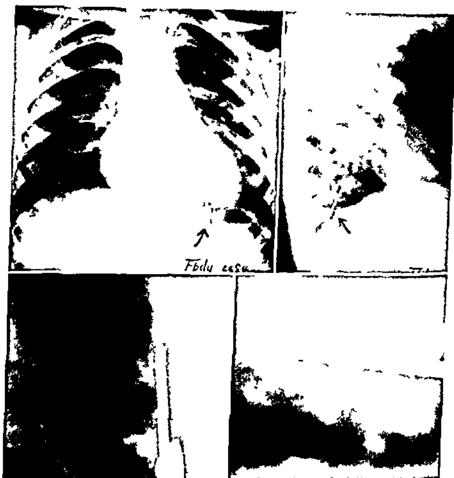


Fig 11 Pin in a peripheral bronchus of left lower lobe Below are shown films taken on the biplane fluoroscopic screen to show the grasping of the point of the pin with forceps introduced through the costophrenic bronchoscope The view to the left shows the anteroposterior or vertical ray view and the film to the right, the lateral or horizontal ray view Incidentally, this patient had been subjected to a laparotomy because of the mistaken diagnosis of foreign body in the stomach perforating the diaphragm! This mistake could not have been made if proper lateral roentgen ray studies had been done

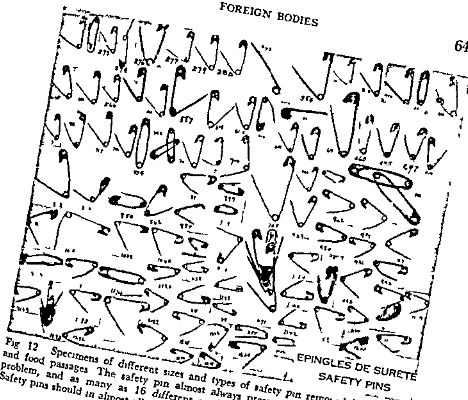


Fig 12 Specimens of different sizes and types of safety pin removed from the air and food passages The safety pin almost always presents some sort of mechanical problem, and as many as 16 different methods of removal have been described Safety pins should in almost all cases be removed under biplane fluoroscopic guidance

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CHAPTER XIII

PLEUROPULMONARY DISEASES CAUSED BY PHYSICAL, CHEMICAL AND THERMAL INJURIES

ACUTE THORACIC INJURIES

By George M Curtis M D and Roy E Swenson, M D

THE SCOPE of thoracic surgery has greatly widened The development of modern inhalation anesthesia, together with the endotracheal ube and its modifications, has made possible a more accurate control of respiration during intrathoracic procedures Too, the development of the newer anesthetic gases, together with the use of helium and positive pressure, have made possible the maintenance of a more satisfactory anesthesia with an adequate alveolar oxygen tension Appreciation of the amount of blood loss, determined by consecutive hemoglobin determinations or by the weighed sponge technique together with its *prompt* replacement, has largely solved the problem of shock and has made more extensive intrathoracic operative procedures possible

More recently the introduction of chemotherapy and the antibiotics has given further impetus to the development of an adequate management of acute thoracic injuries Sulfonamide therapy reduced the incidence and severity of empyema following battle wounds of the thoracic viscera in the recent conflict The sulfonamides, penicillin and its relatives, as well as streptomycin are now in common clinical usage in many thoracic surgery centers Their value in the pre and postoperative management of the thoracic surgical patient is unquestioned The use of such chemotherapeutic agents by *aerosol* inhalation is a more recent addition and is proving to be of value

Progress in the management of other thoracic diseases has also contributed to the facility with which the thoracic surgeon may now cope *with acute thoracic injuries The development of collapse therapy*, incorporating the judicious use of pneumothorax, pneumoperitoneum, phrenic interruption and thoracoplasty, into the therapy of pulmonary tuber

culosis added to our understanding of a disturbed thoracic physiology The rapid strides made in the surgical treatment of bronchiectasis first by cautery pneumonectomy, then lobectomy and more recently by segmental resection, as well as the practical application of pneumonectomy for pulmonary carcinoma have likewise been of great help in developing an experience concerning the nature and effects of acute thoracic injuries, in these instances by an acute surgery

These advances have enabled the thoracic surgeon to manage acute thoracic injuries with a surer knowledge of the disturbed clinical physiology of the thorax

Physiologic Consideration

One of the most significant factors in the management of thoracic injuries is that the organs contained within the thoracic cage function under a pressure less than that of the atmosphere Most thoracic accidents of major concern disturb this relationship Therapeutic measures are consequently designed to restore and maintain it This *negative pressure* is the resultant of two principal factors (*A*) the extensive elastic tissue within the alveolar walls of the lungs which acts to pull them away from the chest wall and (*B*) the serous fluid usually present between the visceral and parietal pleura which creates an *adhesiveness* tending to hold the lungs against the chest wall With each inspiration the chest wall pulls out and away from the lungs, and consequently, the intrathoracic pressure is further lowered while air rushes down the trachea through the bronchi and into the lungs Expiration reverses the *process* and *air is forced out of the lungs and up the trachea*

The lowered pressure during inspiration also exerts a sucking effect on the great vessels and thus draws blood into the great veins and auricles The formation of pleural exudate as well as transudate is likewise affected by these pressure changes During inspiration the lymphatics of the visceral pleura tend to fill later to empty into the pleural space during expiration When the experimental lung is made edematous the rate of pleural fluid formation is dependent upon the force or depth of respiration and the associated pressure changes

Pneumothorax

Introduction of air into either or both pleural cavities results in either partial or complete collapse of the lung on the affected side An *open pneumothorax* occurs if air enters from the outside through a rent in the parietal pleura, *a closed pneumothorax* follows if air enters the pleural

space through a tear in the visceral pleura. Penetrating wounds, either by gunshot or stabbing, usually produce pneumothorax by injuring the parietal pleura. Air enters the chest through the traumatic opening with each inspiration. The size of the opening, governing the amount of air entering with each inspiration, is of the greatest importance since increasing respiratory difficulty develops as the amount of air entering the involved side with each inspiration approaches the vital capacity of the patient.

Tension pneumothorax occurs when air enters the pleural cavity through a traumatic opening, usually in the visceral pleura. A ball valve effect may be thus established, and air is pumped in with each inspiration and cannot escape during expiration. The intrapleural pressure thus increases and causes greater collapse of the involved lung with progressive respiratory difficulty. Hyperpnea, dyspnea and cyanosis ensue. A consideration of the causative injury, physical examination, roentgenography, the symptoms presented, together with measurements of the intrapleural pressure all aid in making the diagnosis.

A flexible partition, the mediastinum, separates the two pleural cavities. When air accumulates in an open pneumothorax, the mediastinum is drawn on inspiration to the uninjured side having the lower pressure. As expiration occurs air escapes slowly through the trachea and hence the mediastinum returns toward the opened side. This to and fro tossing of the mediastinum, which becomes worse as dyspnea deepens, is termed *mediastinal flutter*. Abberations of the normal filling of the great veins and auricles occur and circulatory embarrassment may develop. Moreover, the to and fro motion of the mediastinum lessens the oxygen exchange in the lung of the *uninvolved* side. With expiration, some air from this lung enters the partially collapsed lung on the involved side, later to reenter the uninvolved lung with the next inspiration. Brauer termed this useless transfer of air from one lung to the other "*Pendelluft*."

The treatment of uncomplicated pneumothorax consists in the prompt closure of the traumatic opening followed by aspiration of the air within the pleural cavity. This enables prompt reexpansion of the lung. If a small tear in the lung is present, the opening in the chest wall should first be closed, a small rubber catheter then inserted and its distal end connected to a water seal drainage bottle. If the air is not withdrawn rapidly enough by this method greater suction may be applied from the

ordinary 3 bottle apparatus for gastric suction or even by the use of a controlled Stedman pump

Emphysema

Subcutaneous emphysema may develop after lung injury with an accompanying tearing of the parietal pleura Air escapes from the lung and then through the torn pleura and out into the peripheral tissue spaces This may occur when the lung is adherent to the chest wall and even in the absence of a pneumothorax Emphysema of this type is usually associated with the fracture of one or more ribs The local emphysema may spread and even become widely generalized *Mediastinal emphysema* is a more serious complication and is most apt to occur after injury to the trachea or one of the larger bronchi Air then travels throughout the mediastinum and may even rapidly dissect its way into the neck The dangerous effects of this type of emphysema arise when the increasing volume of air, with the force of a labored inspiration behind it, exerts pressure upon the great veins within the base of the neck and mediastinum If significant pressure symptoms develop, together with dyspnea or cyanosis, emergency mediastinotomy from just above the sternum, with the insertion of a soft drain, is indicated

Emphysematous air is usually slowly absorbed without ill effects The treatment of subcautaneous emphysema is conservative, and usually is preventive, in maintaining maximum lung expansion so that the leak will seal to the parietal pleura and heal spontaneously The insertion of a soft rubber catheter into the pleural cavity and the application of suction is usually sufficient If such conservative therapy proves inadequate, thoracotomy with closure of the leak under direct vision is indicated This also applies to ruptured bronchi

Hemorrhage

Injuries disrupting the continuity of the chest wall may be extr-- and/or intrathoracic The former involves tissues exterior to the parietal pleura, while the latter includes the heart, pleura, lungs and diaphragm Penetrating wounds usually pierce the chest wall, tear the pleural coverings and involve the lungs or mediastinal structures Such traumatic wounds may involve arteries located superficially or deep in the thorax

Hemorrhage from the internal mamary or intercostal vessels may be of three general types

1 Frank and obvious hemorrhage that may be controlled by pack ing or by application of a hemostat and ligature

2 False aneurysm with subpleural hematoma and infiltration with delayed external hemorrhage

3 Wounds associated with pleural tears and continued intrapleural hemorrhage These usually produce the signs and symptoms of a rapid increase in intrapleural pressure together with mediastinal shift Death usually ensues unless the severed artery is ligated It is well to remember *that the internal mammary arteries should be ligated above and below* the bleeding point because of their double blood supply Similarly large secondary external hemorrhage and signs of progressive hemothorax de mand exploration and careful ligation of the vessels involved

Hemorrhage from the axillary artery with the resultant development of a false aneurysm is usually manifested by a local pulsating mass asso ciated with evidence of the nerve injury to the axillary cords This may be due either to direct damage from the wounding agent or to pressure from the enlarging hematoma This injury demands exploration in a well equipped operating room as well as adequate facilities for the replacement of blood loss The primary principle in the treatment of this wound is to obtain sufficient exposure of the axillary artery and vein above and below the aneurysm before ligation is attempted Frequently arteriovenous aneurysm may be present If so the venous aneurysm must also be excised

The signs of injury to the *subclavian artery* are similar to those of the axillary artery however the hematoma lies more deeply and the result ant signs are not as clear A bruit during cardiac systole is usually pres ent or is heard throughout the cardiac cycle if an arteriovenous aneurysm is present *In this latter case an elevation of the venous pressure in the* arm of the involved side is usually present False aneurysms in this region are hazardous surgical problems and are best managed by experi enced surgeons in adequately equipped operating rooms

False aneurysm of the *innominate artery* is a catastrophe of the first magnitude characterized by pain beneath the sternum and in the cervi cal region Roentgenography reveals infiltration of the superior media stinum as well as induration extending up into the suprasternal notch Since the surgical approach to such lesions is difficult and severe it is wise to rule out superficial lesions prior to an attempt at surgery Explo ration is carried out through a T incision the top of which transects above the suprasternal notch The vertical incision bisects the sternum

which is later split by the use of a wire saw and then retracted to give adequate exposure

Hemothorax and Hemopneumothorax

The presence of blood and/or air in the pleural cavity is the most common cause of anoxia following injury to the chest The amount of functional pulmonary tissue is so reduced that adequate gaseous exchange between the alveoli and the blood stream cannot occur The individual responsible for the management of such patients must realize that relatively slight respiratory embarrassment may be of major import in the patient who may also have suffered a large blood loss tissue trauma and perhaps other severe wounds If the respiratory embarrassment is severe, immediate thoracentesis is advisable Should it be inadvisable to move the patient or to have him sit up, thoracentesis may be done in the axillary region for the removal of fluid and through the anterior chest wall for removal of the air

When dyspnea and respiratory embarrassment are not complications of the hemothorax, thoracentesis for withdrawal of blood is usually done two to five days after injury The problem of subsequent air replacement in the treatment of hemothorax is subject to considerable debate Devised by Morelli, and later developed by Foster to control hemorrhage from the bleeding lung this method consists of the intrapleural injection of a volume of approximately ⅓ more air than the fluid withdrawn Compression of the lung by the resultant pneumothorax is most useful in controlling hemorrhage from its peripheral portion, and deserves a trial in attempting the control of active pulmonary bleeding However more recent experience in World War II has shown that once active bleeding has ceased excellent results are secured by the slow withdrawal of blood from the hemothorax, thus permitting the lung slowly to reexpand Two to five days after injury, from 300 to 700 cc of blood may be slowly withdrawn by thoracentesis Withdrawal is stopped abruptly, however, if the patient develops a 'tight' feeling or pain in his chest Aspiration is then repeated every day or two until the lung is as completely reexpanded as possible

There are two disadvantages to early reexpansion of the lung the greatest of which is the possibility of starting fresh pulmonary hemorrhage A lesser danger is the possibility of introducing infection into the hemothorax with repeated thoracenteses Recurrence of hemorrhage after withdrawal of blood was found to be a rare complication If hem

orrhage does recur splinting of the lung by the introduction of pneumothorax should be advantageous The use of an aseptic technique, the sulfonamides and the antibiotics are helpful in preventing the development of empyema They may be given systemically as well as injected into the hemothorax

Foreign Bodies in the Thoracic Cavity

Opinions regarding the management of foreign bodies within the thorax vary from an ultraconservative 'hands off to a decision for immediate removal Somewhere between these two poles of surgical opinion lies the rational approach to the problem Blades and Dugan state that if a patient has survived the immediate effects of gunshot wound, neither the size nor position of the retained foreign body should demand immediate emergency surgery It would seem that this statement could be paraphrased to include any type of chest wound that has resulted in the retention of a foreign body It seems wiser to prepare carefully such a patient with chemotherapy, blood transfusions, etc and make the suitably planned operative procedure an elective one The question of the timing of surgical intervention varies from patient to patient, and it is most difficult to apply any dogmatic rules of thumb It is largely a matter of experienced surgical judgment

Large foreign bodies in the lung are apt to produce cough and a mucoid type of sputum Johnson noted no influence of retained foreign bodies on the course of the wound 'The incidence of hemothorax as opposed to simple lung trauma was the same whether the missile traversed the chest cavity or stopped within it He noted no significant difference in the incidence of empyema However the retention of a foreign body within the lung substance frequently becomes the center of an infected cavity, draining either into a bronchus, or the pleural cavity The development of a lung abscess is thus likely Since a foreign body encysted within the lung becomes a center of granulation tissue activity, the elective removal of foreign bodies measuring from 1 0 to 1 5 cm or larger in any diameter has been recommended

The Traumatic Wet Lung

Following injury to the chest, many factors contribute to the abnormal accumulation of fluids within the respiratory tract Such fluids interfere with the normal gaseous exchange between the alveolar air and the blood stream Sufficient fluid may accumulate to completely block the airway to various segments of the lung Atelectasis, varying from

lobular to segmental, or from lobar to massive collapse of an entire lung, may occur Various forms of pneumonia are also apt to develop *in such a favorable environment*

De Takats and his associates have experimentally shown that trauma to the chest wall is followed by *bronchospasm* together with an increased bronchial secretion in 60 per cent of the experimental animals so injured Following chest injury, excessive production of mucoid secretion *from the tracheobronchial tree is frequently observed Mucopurulent* secretion from a secondary bronchitis or bronchopneumonia may also be present as may secretions resulting from upper respiratory tract infections

Intrapulmonary hemorrhage frequently results in the presence of blood in the tracheobronchial tree This in itself is a mechanical factor tending to obstruct the respiratory tract, but in addition, the presence of blood in the airway also acts as a chemical factor, irritating the bronchial mucosa *This irritation, in turn, becomes responsible for greater* secretion by the bronchial glands Blood from the hemothorax may be present in the bronchi if a bronchopleural fistula exists Similarly, the purulent products of an empyema may find their way into the pulmonary tree and add the complication of infection to the already pressing problem of obstruction

The alveoli may fill with fluid The local outpouring of plasma at the site of injury is a frequent contributing factor Obstruction of the tracheobronchial tree is usually followed by the production of pleural and/or pulmonary exudate and/or transudates Anoxia is also a frequent etiologic agent in the accumulation of alveolar fluid Severe in*spiratory movements may also abet such accumulations of fluid*

Roentgenography of the chest is not of too great aid in the evaluation of the *wet lung* since the pulmonary shadows are frequently obscured by the other chest injuries or by an *hemothorax A continuous* cough, productive of a scant, watery sputum, is an early sign of the accumulation of fluid in the pulmonary tree, and of poor bronchial drainage Varying degrees of dyspnea are present, respirations are usually shallow and jerky, and for the most part ineffectual, being limited by the pain associated with each inspiratory effort Rales are usually present and are best heard after coughing Late signs are severe dyspnea cyanosis, shock, audible rales, anoxic psychoses and eventually coma A mucoid sputum is usually present, it becomes purulent if infection supervenes, either from a pneumonic process or from an empyema

through a bronchopleural fistula. Blood or clots in the sputum suggest recent or old pulmonary hemorrhage, a serosanguineous sputum suggests an hemothorax with bronchopleural fistula

Intercostal nerve block using 5 to 10 cc. of 1 to 2 per cent novocaine injected around the intercostal nerves supplying the traumatized area has been found of great value The injection of several nerves above and below the injured area is of great benefit Intercostal block is of great value in the relief of pain arising from the chest wall and pleura Once the pain is relieved, inspiration becomes deeper, and *cough with less pain* becomes possible It is then feasible to encourage the patient to cough and empty the pulmonary tree

Intratracheal aspiration with a 16 or 18 urethral catheter attached to a device capable of delivering sufficient negative pressure is also useful Aspiration by tracheal catheter is frequently an emergency procedure which must be done before other methods can be safely attempted Those responsible for such patients are referred to Cameron Haight's excellent paper on this subject Aspiration of the lower pulmonary tree may be accomplished by bronchoscopy followed by aspiration through the bronchoscope This is more thorough than tracheal catheter aspiration Administration of 100 per cent oxygen under positive pressure is also of great benefit in the management of pulmonary edema The aim of such therapy, after the tracheobronchial tree has been as completely aspirated as possible, is to permit sufficient oxygen to reach the bronchioles, and consequently the alveoli, to oppose the hydrostatic pressure of the blood stream, and to make possible a more complete oxygenation of the blood Positive pressures of from 2 to 6 cm of water are usually safe in such cases This pressure should never approximate 10 cm of water The systemic administration of concentrated serum albumin may raise the osmotic pressure of the blood proteins sufficiently to aid in returning extravasated plasma from the alveoli

Blast Injuries

Injury to the lung without external evidence of trauma is occasionally seen in civilian practice, and more frequently observed in military practice where the personnel are exposed to the blast effects of high explosives Following cave ins and automobile accidents, injury to the lung may occur without obvious damage to the chest wall Compression of the lung occurs subsequent to the initial blow which is strong enough to compress the resilient thoracic cage, yet does not break the skin or

occurs, the retropleural chyle then ruptures into the pleural space to produce a chylothorax Most chylothoraces develop on the right side since the duct lies on the right for two thirds of its course through the thorax

Chylothorax secondary to trauma usually develops from two to ten days after the injury Following the accumulation of chyle, dyspnea, and signs of shock or collapse develop Following thoracentesis, chyle re accumulates The loss of serum proteins and fats in the chyle is followed by inanition, oliguria, thirst and emaciation The determination of fat in the chylous fluid is pathognomonic Chylous fluid is usually milky white in appearance, if allowed to stand in a test tube, a creamy layer may develop on the top, its specific gravity is usually greater than 1 012, its fat content varies from 0 4 to 4 0 per cent, if alkalinized and shaken with ether, the milky fluid will clear, Sudan III will stain the fat orange, and osmic acid will stain it black The roentgen picture is similar to that of an hemothorax

Treatment of traumatic chylothorax has been unsatisfactory, and the mortality rate is approximately 50 percent Open thoracotomy and repair of the duct has not been successful Thoracentesis and aspiration of the chyle is necessary for relief of repiratory difficulty, but this results in depletion of body protein and fats The return of this fluid by sternal or intravenous transfusion is not without danger Death has been re ported following this procedure X ray therapy is not of great value Since experimental ligation of the thoracic duct is not followed by the development of chylothorax, it would appear that thoracotomy and liga tion of the duct above and below the site of rupture would offer better results than attempts at repair

Thoracoabdominal Injuries

The term *thoracoabdominal wound* implies simultaneous injury to the abdomen and thorax by the same object Penetration through the diaphragm or transmission of a sufficient force across the diaphragm with resultant injuries in both serous cavities is also implied Before surgery of any type is attempted shock and blood loss must be corrected Thoracic physiology should be restored to as normal a condition as possible and permitted to stabilize for a short while before surgery If an hemothorax or pneumothorax exists it should be corrected If thora cotomy is required to restore the respiratory mechanism to normal, it should be done before the abdominal exploration Frequently, wounds

of the upper abdomen can be satisfactorily explored from above, through a transthoracic incision Exploration through the thorax permits irrigation of the thorax after the diaphragm has been closed Blood and clots can also be removed from the pleural cavity Once some semblance of respiratory balance is restored exploration of the abdomen is indicated when a missile has penetrated through the body from the level of the twelfth rib posteriorly to the level of the fourth rib anteriorly Most combined thoraco-abdominal wounds are obvious, but if doubt exists exploration is indicated Reconstructive surgery of the chest or abdomen can be attempted after the threatening physiological aberrations of the chest and abdomen have been corrected The management of such complex injuries is a major surgical problem Readers are referred to the papers of Betts and of Shefts and Doud

Acute Cardiac Injuries

The prognosis following trauma to the heart and mediastinal structures is not as gloomy as in former years Wounds of the heart are usually caused by knife ice pick or bullet Stab wounds of the pericardium and heart can be successfully sutured after mediastinotomy If death does not occur immediately following such injuries, *cardiac tamponade* usually develops The term cardiac tamponade was introduced by Rose in 1884 and when strictly defined means compression of the pericardial contents by increased intrapericardial pressure Tamponade of the heart may be due to the presence of exudates transudates or to blood in the pericardial sac The rate of accumulation of such fluid is of great importance Approximately 150 to 200 cc of fluid can be present before untoward effects develop Experimentally the auricles of the heart are compressed as soon the intrapericardial pressure exceeds that of the great veins Sudden introduction of fluid into the pericardium of the dog is followed by a drop in the blood pressure in the femoral artery and a rise of the pressure in the jugular vein if the fluid is allowed to escape rapidly the arterial pressure rises and the venous pressure drops to zero During tamponade the coronary veins fail to fill properly If uncorrected, heartblock develops and death supervenes During tamponade patients complain of compression in the region of the heart or of substernal discomfort Pain mimicking the anginal syndrome, radiating to the left shoulder and down the left arm, may also be present Dyspnea is usually obvious, as is cyanosis of the neck and head The great veins of the neck are usually prominent Initial tachycardia is usually fol

lowed by a weak, thready pulse Coma and death from heart block and anoxia supervene if therapy is not given

The therapy of cardiac tamponade caused by hemorrhage secondary to injury of the heart is rapid mediastinotomy, incision into the pericardium and suture of the heart wound

Nevertheless, effects similar to the presence of fluid in the pericardial cavity may be caused by inadequate filling of the auricles due to other pressures and tractions The causative mediastinal displacement may be due to pressure pneumothorax, hemothorax, massive atelectasis, diaphragmatic hernia and emphysema, or hematoma of the mediastinum If compression of the great veins and auricles is secondary to tension pneumothorax, the insertion of a needle into the pleural space is usually followed by dramatic improvement Similarly if such compression is secondary to massive atelectasis, the mediastinum being drawn to the involved side, the institution of a small pneumothorax on the involved side will aid in controlling the immediate cardiac problem Later, when the general condition of the patient has improved, bronchoscopy and aspiration of the tracheobronchial tree can be done to relieve the obstruction, the lung reexpanded and the small pneumothorax removed Mediastinal hemothorax or emphysema causing pressure upon the auricles or great veins is relieved by an incision at the suprasternal notch, permitting blood and air to escape from the distended alveolar tissue within the medistinum Should a diaphragmatic hernia be the cause of such pressure, repair is indicated

Contusion of the heart may occur subsequent to any compression of the midportion of the anterior chest wall Common causes of this injury are blasts, steering wheel accidents and cave ins Complete or partial sterno chondral separation may result in depression of the sternum and exert pressure upon the heart Cardiac contusions frequently follow such accidents Those surviving such cardiac trauma exhibit transient collapse, complain of precordial pain, dyspnea and palpitation The anginal syndrome may also be present A pericardial effusion usually accompanies such a lesion The treatment consists of extended bed rest, and this is particularly so in the *symptom free period* following the initial collapse and pain, if coronary occlusion and cardiac rupture are to be prevented

If a patient survives the initial injury to his thorax or thoracic cavity, and reaches a hospital possessing facilities for and personnel trained in the management of thoracic cases, he should not die of his chest wound

unless he develops an overwhelming pulmonary infection or has some unusual accident Similarly, complications such as empyema and untoward respiratory disturbances should not develop if adequate therapeutic measures are instituted in time

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PNEUMOPATHIES RESULTING FROM CONFLAGRATION

By ANDREW L. BANYAI, M D AND J WINTHROP PEABODY, M D

Inhalation of large amounts of smoke, fumes and gases in a confined space, which result from the burning of wood, paper, textile, leather, paint, varnish and other inflammable material, is bound to produce varying degrees of damage to the respiratory tract These pathologic changes are usually, but not always, associated with skin burns of various extent and severity and often with signs of shock In this connection, it may be mentioned that extensive skin burns do not necessarily imply coexistent involvement of the air passages

The postmortem findings have been accurately described by Beckey and Schmitz, Fischer and Goldschmid and by Finland and his associates They noted that an extensive, diffuse, edematous, pseudomembranous inflammation involved the larnyx, trachea, bronchi and bronchioles, extending down to the finest ramifications In addition to mucosal hyperemia, there are petechial or confluent hemorrhages on the mucosal surface and in the submucosa Considerable necrosis may be present in the walls of the bronchi and bronchioles, with ulceration The pseudomembrane is covered with brown or black tenacious mucoid material The smaller bronchi are dilated by air entrapped distal to a partial occlusion which permits the ingress of air but blocks its egress A great many of the bronchioles are filled with fibrin plugs This results in atelectasis of the smallest respiratory units, the lobules This atelectasis is of the miliary type Occlusion of some of the bronchi is a common occurrence which leads to patchy atelectasis A check-valve like bronchial stenosis with free entry but no outflow of the air is followed by patchy emphysema In some areas, the alveoli are filled with viscid, serous exudate which contains fibrin, red blood cells histiocytes and plasma cells There are scattered areas of congestion, and in some cases, thrombosed blood vessels and pulmonary infarction Pulmonary edema is very rarely a dominant manifestation Bronchopneumonia, simple or hemorrhagic is an unusual occurrence Extensive pneumonic consolidation is seen only exceptionally Occasionally, small abscesses are present

According to Finland and his associates, these pathologic changes resembled those found in victims of the Cleveland Clinic disaster which resulted from the inhalation of nitrous fumes of burning nitrocellulose x ray films Also, these authors observed that there was a

close correlation between the loss of consciousness and the degree of damage to the respiratory tract Individuals who become unconscious in a burning building and are not promptly removed, are bound to inhale large amounts of hot, noxious gases and consequently develop severe pulmonary disease Moreover, Finland and his associates noted frequent parallelism between the extent of surface burn and the severity of the concurrent pulmonary lesion Infection seems to play a minor role, if any, in the pathologic changes Of the micro organisms found in the bronchial secretions, staphylococcus aureus appears to be the most likely contributing agent

Symptomatology

Local and general symptoms are observed in patients who inhaled large amounts of fumes and gases resulting from conflagration Great variations may be noted in the intensity of symptoms depending upon the extent of pulmonary damage and the co-existent surface burn Following massive inhalation of products of combustion the odor of smoke on the patient s breath may be noticeable for hours Hoarseness is frequent and often, it is marked Also sore throat is common and in some instances, it is associated with dysphagia Wheezing is a prominent symptom Stridor is present in victims of heavy exposure when they are first seen or it develops a few days later It may be persistent or recurrent Some individuals with severe damage of the air passages have an intermittent, rapid, shallow respiration which may become progressively worse until fatal termination In some patients, dyspnea and cyanosis are not evident immediately after the accident but become manifest on the third or fourth day of hospitalization There are great variations in the intensity of cough It may be slight moderate or severe it is constant or paroxysmal, and may last from a few days to a few months The cough is productive of scant, thick, viscid, mucoid sputum, black with soot and sometimes blood tinged or containing frank blood In some cases, it changes into profuse, mucopurulent or purulent expectoration it may assume a diffuse bloody appearance or a rusty color Cough may persist for months after clearing of roentgenologically demonstrable lung changes Occasionally, after great difficulties, the patient expectorates pieces of fibrinous pseudomembrane Pain and soreness in the chest are often complained of

The general symptoms include occasional chills, fever which may range from 101 to 104° F , and terminally may reach from 105 to 109°

Fever is entirely absent in patient with slight involvement of the respiratory tract and with limited or no surface burns Vomiting is not infrequent In consequence of extensive surface burns, shock is of common occurrence When first seen, the patient may be restless due to pain or cerebral changes He may be disoriented, irrational, stuporous or in coma

Diagnosis

There are substantial gradations in physical and x ray findings proportionate to the extent, severity and location of pathologic changes in the respiratory tract Inspection of the pharynx reveals congestion and edema Usually there is evidence of laryngitis The percussion note over the lungs may be unchanged or hyperresonant The latter results from partial bronchial occlusion which prevents the escape of accumulated air from areas distal to stenosed bronchi Also, percussion may reveal segmental atelectasis Limited areas of dullness caused by the latter may be transient or migratory in character They may alternate with circumscribed hyperresonant percussion note indicative of patchy emphysema Atelectasis is more common in the posterior, dependent portions of the lung than elsewhere Evidence of massive atelectasis is rarely encountered In such cases, the corresponding hemithorax is reduced in size and its respiratory excursions are absent At the same time, dull percussion note and absence of breath sounds are noted over the involved lung

Edema and formation of pseudomembrane in the bronchi, deposition of exudate and fibrin in the bronchi, bronchioles and alveoli are recognized by the presence of sonorous and sibilant rales and fine and medium "moist rales Rales are usually widely distributed over both lungs Findings characteristic of bronchopneumonia or lobar inflammatory consolidation, are the exception rather than the rule There is no definite sequence in the development of pathologic changes responsible for the abnormal physical findings Consequently, some patients may show high or low pitched musical rales first, then crepitant rales of varying sizes In others, fine or medium sized "moist rales are detected prior to the appearance of rhonchi One of the typical manifestations of this condition is that marked fluctuations in the physical findings occur during the course of the disease Rales are often present in patients with normal x ray findings and may disappear in from a few days to a few weeks The breath sounds are diminished over areas of segmental atelectasis This change, however

close correlation between the loss of consciousness and the degree of damage to the respiratory tract Individuals who become unconscious in a burning building and are not promptly removed, are bound to inhale large amounts of hot, noxious gases and consequently develop severe pulmonary disease Moreover, Finland and his associates noted frequent parallelism between the extent of surface burn and the severity of the concurrent pulmonary lesion Infection seems to play a minor role, if any, in the pathologic changes Of the micro organisms found in the bronchial secretions, staphylococcus aureus appears to be the most likely contributing agent

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is often transient on account of the shifting nature of the underlying pathologic alterations In patients whose pulmonary condition be comes progressively worse, rales become more and more numerous and persist until death Accumulation of large amounts of exudate in the pharynx and larynx causes gurgling noises

Roentgenologic findings in persons with pneumopathies resulting from conflagration have been reported by several clinicians The ex cellent observations of Schatzki can be summarized in the following points

(1) The earliest changes are asymmetrically radiating bands and lines from both hilar regions, large areas of homogenous densities and miliary shadows representing miliary atelectasis, the latter caused by plugging of minute bronchi Miliary atelectasis may be present in one or two lobes or throughout both lungs

(2) Atelectasis may be visualized in the form of small triangular or round shadows or as bands and linear densities which occupy a horizontal oblique or vertical position

(3) Rarely, lobar atelectasis is seen in one or both lower lobes This is associated with elevation of the corresponding hemidiaphragm slight mediastinal shift and a downward displacement of the ipso-lateral hilar structures There is no mediastinal shift in bilateral lobar atelectasis

(4) Lobar or segmental emphysema is characterized by localized increase in radiotranslucency The presence of entrapped air is best demonstrated in an expiratory roentgenogram

(5) Areas of circumscribed atelectasis and emphysema may be seen simultaneously in the same individual

(6) Pulmonary edema is usually observed as a terminal phenom enon It is denoted by diffuse haziness of both lung fields

Finland, Ritvo and their associates commented on the fairly close relation between x ray findings and the severity of symptoms They noted the frequent enlargement of hilar shadows, increase in the bronchovascular markings and occasionally the occurrence of homo genous, ground glass appearance of one lobe or a large portion of one lung, signifying "drowned lung," that is, the presence of fluid in par tially atelectatic areas These changes usually cleared rapidly Such rapid clearing was also observed in cases of pure atelectasis and in atelectasis associated with localized emphysema Sudden changes in roentgenologic findings were particularly obvious in some patients who

were treated with tracheotomy or in whom respiratory obstruction was relieved by aspiration The clearing of extensive, patchy roentgenographically observed lesions requires from one to three weeks

Laboratory examinations may reveal important contributory information, particularly in the presence of extensive surface burn Leucocytosis should not be interpreted as direct proof of coexistent pulmonary infection, for it occurs as the result of skin burn alone In patients with extensive surface burns, there is hyperproteinemia, with concomitant increase in hemoconcentration Finland and his associates measured the vital capacity of the lung in these patients They recorded values ranging from 25 to 88 per cent of normal and noted appreciable increase with improvement in the pulmonary condition in most of them Examination of the sputum reveals ciliated cells, tissue debris, fibrin and possibly fragments of pseudomembrane One may identify hemolytic and nonhemolytic streptococci, pneumococci and sometimes, staphylococcus *aureus or other micro organism* Some of them are present in the normal microflora and are not considered responsible for the pulmonary disease

Prognosis

The fate of patients exposed to conflagration is greatly influenced by the severity and extent of the surface burn, by the damage suffered by the respiratory passages and also, depends upon the promptness and adequacy of treatment Concerning this subject, reference should be made to the observations of Finland and his associates who treated a large group of patients following the Cocoanut Grove Disaster in Boston, Mass They state that all of the deaths occurred in two types of cases

(1) Individuals with burns which involved 30 per cent, or more of the body surface,

(2) Persons with the severest type of respiratory symptoms, particularly with evidence of marked obstruction of the respiratory tract There were only two recoveries in the first group of 22 patients, and only three recoveries in the second group of 30 cases. The average time of survival for all fatal cases was nine days Temporary or permanent improvement may follow tracheotomy, tracheotomy and suction through the tracheotomy tube, and tracheotomy and suction through a bronchoscope inserted through the tracheotomy wound These measures, even when carried out promptly, may not save the patient's life in case of extensive surface burn or severe damage to the

lower air passages. The same authors observed also, that almost all of the patients died, whose temperatures were over 104 degrees during the first few days. Moreover, high mortality was recorded in individuals whose leucocyte counts were above 15,000 during the first week after the burns were sustained. They expressed the view that administration of antibiotics in adequate doses is likely to obviate or counteract infection with pathogens and thus improve life expectancy.

Treatment

The treatment of patients with thermal or chemical burns of the respiratory tract, with or without associated surface burns, consists of the following measures:

1. Attention to shock.
2. *Correction of respiratory embarrassment.*
3. Treatment of surface burns.
4. Specific and palliative measures.

Shock is combatted by restoring the blood volume and crystalloid balance of body fluids. There is incontrovertible evidence of the value of plasma for this purpose.

A quick, simple and practicable method for calculating the plasma needed, is based on Berkow's formula of percentage of body surface burned. Fifty cubic centimeters of plasma should be given for every 1 per cent of body surface affected by a deep burn. Of the total surface area of the body, the trunk represents 38 per cent, one arm 6.75 per cent, one thigh 9.5 per cent, one leg 7 per cent, one foot 3 per cent, and the head, 6 per cent.

In patients with severe pulmonary damage, there has been a great deal of hesitancy concerning the advisability of giving large doses of plasma, dextrose solution and isotonic solution of sodium chloride. The experience of Finland and his associates has shown conclusively, that in the absence of pulmonary edema, the administration of large amounts of plasma and fluids is valuable, and that it does not lead to the aggravation of the pulmonary damage, or to an increase in the respiratory symptoms. According to their precept, the dosage of plasma and fluids should be adapted to the condition of the patient. They found that some of their patients required as much as 3,250 cc. of plasma (250 cc. of plasma = 1 unit) in addition to 200 cc. of 25 per cent solution of albumin (the osmotic equivalent of 1,000 cc. of plasma) and 1500 cc. of fluids orally within the first 24 hour period. Others were

given 2,500 cc of plasma (10 units), 4,500 cc of isotonic solution of sodium chloride intravenously, and 2,300 cc of fluids orally during the first day of treatment Also, they used large amounts of 5 per cent solution of dextrose intravenously in addition to adequate doses of plasma and isotonic solution of sodium chloride The administration of dextrose and sodium chloride solutions once or twice a day is continued until oral intake of fluids is adequate

It is known that adrenal cortex extract decreases capillary permeability and loss of plasma, sodium and chloride For this reason, it is considered a good adjunct to combatting shock Adrenal cortical extract is given either intramuscularly or with plasma transfusion or with infusion of dextrose or isotonic solution of sodium chloride Eschatin (Parke, Davis & Co) is a useful adrenal cortex hormone preparation for this purpose It is administered in doses of 5 to 10 cc every four to six hours for adults

Goldenberg and his collaborators recommended intravenous infusion of nor epinephrin (nor adrenalin, arterenol) for combatting shock They report that in addition to its general pressor action upon the peripheral vessels of the greater circulation, nor epinephrin causes a pronounced increase in the coronary blood flow

In addition, the following points should be observed in the management of the patient in shock

1 Close check should be kept on water, plasma and electrolyte balance Fluid intake and output should be measured and laboratory examinations of the blood should be carried out whenever circumstances permit This work includes determination of hemoglobin, red blood cells, hematocrit as often as circumstances require

2 Frequent blood pressure determinations

3 Plasma is to be given by continuous infusion, preferably by the drip method Plasma may be given with equal amount of 5 per cent dextrose solution

4 Progressive increase in hemoconcentration calls for more plasma

5 When plasma volume is restored and shock has been relieved, the administration of plasma is discontinued and is followed, if necessary, by infusion of 5 per cent solution of dextrose or isotonic solution of sodium chloride

6 Special attention should be paid to the prevention and alleviation of possible liver damage, by maintaining adequate urinary output

7 If no vomiting is present, the patient should be given from 3,500 to 4,000 cc of fluids by mouth during a 24 hour period to replace water lost through urinary output, insensible perspiration, evaporation through the lung and through weeping areas of the burned skin

8 Liberal fluid intake is one of the best means for liquifying and loosening inflammatory exudate in the air passages and thereby facilitating expectoration

9 Following recovery from shock, low hemoglobin and red blood cell count require transfusion of whole blood and other appropriate corrective measures

Respiratory embarrassment should be relieved immediately Therapeutic measures are selected according to the cause and gravity of the situation

1 Accumulation of mucus and inflammatory exudate in the pharnyx, larynx and trachea, is removed by suction In this fashion stridor and choking spells may be relieved

2 Dyspnea, cyanosis and increase in hemoconcentration call for the administration of oxygen The latter is supplied in the commercially available 220 cubic foot size cylinders, and is given either through a well fitting mask, oropharyngeal catheter, or in a tent When the gas is inhaled through an oropharyngeal catheter, inserted through the nose, and the flow meter is set at 10 to 12 liters per minute, from 50 and 65 per cent oxygen can be attained in the air inhaled This method may be used for weeks if necessary The catheter is well lubricated with some anesthetic ointment prior to insertion and it is so placed that swallowing of oxygen and irritation of the inflamed pharnyx are avoided The catheter is changed from one nostril to the other every 24 hours Oxygen inhalations in a tent, using 10 liters of 100 per cent oxygen per minute, are given continuously Due to unavoidable leakage, the concentration of oxygen within the tent is usually from 50 to 70 per cent Partial face masks, such as the B L B nasal mask or the B L B oronasal mask and similar equipment, is adjusted so that from 6 to 8 liters of 100 per cent oxygen is delivered to the patient In these instances, the gas actually inhaled is less than 100 per cent oxygen on account of unavoidable leakage of outside air into the mask Even so, satisfactory supply of oxygen can be maintained by this means Oxygen may be administered through these masks without interruption and without any discomfort to the patient for a 48 hour period When inhalations through a mask are

discontinued for 30 minutes, four to five times a day, the treatment may be continued safely for weeks if necessary

3 Helium oxygen mixture, in a proportion of 75 per cent helium and 25 per cent oxygen, is of value in cases where excessive amounts of exudate or swelling of the respiratory mucosa prevents the free access of air to the alveoli On account of the low density of helium as compared to that of oxygen and nitrogen, the inhalation of this mixture requires only one half the respiratory effort used for inhaling air or 100 per cent oxygen Also, because of its lower density, this mixture reaches the alveoli through narrowed air passages more readily than either air or oxygen does It is expedient to give helium oxygen mixture under positive expiratory pressure of 3 to 6 cm of water through a hood or mask

4 Inhalation of a mixture containing 5 per cent carbon dioxide and 95 per cent oxygen is the most effective means for liquifying inflammatory exudate in the respiratory tract The liquified exudate is easily expectorated or resorbed by the blood stream Thus, ridding the respiratory tract of accumulated inflammatory products, free access of air to the alveoli is restored and dyspnea relieved When carbon dioxide is used, there is no need for the administration of other expectorant drugs or inhalants Their influence is inferior to that of carbon dioxide In addition to its liquifying action on mucus, carbon dioxide is a stimulant of the respiratory center in the medulla Consequently, it is capable of changing a rapid, shallow respiration in patients with shock, into deep respiration In this fashion, it is bound to improve the functional capacity of the lungs and restore the ventilation of atelectatic areas Patients with shock are in a state of acapnia (lack of normal amounts of carbon dioxide) This is brought about partly by occlusion of the air passages by exudate and mucosal swelling and partly by deflation of the lung due to pain resulting from burns or trauma Lowering of the carbon dioxide content of the blood deprives the body of its normal respiratory stimulant The administration of carbon dioxide, therefore, is necessary in such cases so as to assure normal functional balance of the respiratory center Individuals exposed to conflagration in confined spaces easily develop carbon monoxide poisoning Inhalation of carbon dioxide causes a rapid elimination of carbon monoxide from the blood by increased respiration and by its replacement in the blood by oxygen Depending upon the requirement of the case, carbon dioxide inhala

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CHAPTER XIV

ATELECTASIS

By E W Hayes, M D and E W Hayes, Jr M D

Definition

ATELECTASIS, literally, means imperfect expansion The word is derived from two Greek words, *ateles*, meaning imperfect, and *ektasis* meaning expansion According to Pinner, the term atelectasis should be used only to designate an airless condition of the lung where re expansion to a normal state is possible In our discussion we will employ the term in this way

Atelectasis develops under two circumstances First, complete bronchial obstruction and second, intrapleural pressure that remains higher than atmospheric pressure during both phases of respiration Under these conditions no air can enter the alveoli and the air already there is absorbed into the blood if the capillary circulation is not damaged Atelectasis is a reversible condition in that if and when the cause is removed reexpansion of the lung takes place When in fection with inflammatory exudate, edematous fluid or fibrous tissue develop in place of the absorbed air, though the initiating phase may have been atelectasis, the resulting condition is pneumonia pulmonary edema or pulmonary fibrosis, respectively, the complications or sequelae of atelectasis

In pulmonary atelectasis, a portion of a lobe, a lobe, two or more lobes, a whole lung or both lungs may be airless

History

The recognition of the condition which is known today as atelectasis began in the early part of the nineteenth century Schenk is given credit for the first description, in 1811, of the condition as he found it in the lungs of children dying at or soon after birth He did not call the condition atelectasis but described these lungs as appearing to have never been inflated, as being solid, and sinking when

placed in water Louis, in 1829, distinguished collapse of the lung from pneumonia in adults and termed it carnification Georg, in 1835, in working with infant lungs, used the word atelectasis for the first time to describe the condition of the lungs he found in some of these cases Bowen gives Rilliet and Barthez of London credit for the first mention, in 1841, of the collapse of a whole lobe In describing what was then termed carnification of infants' lungs, they stated that the middle lobe was the only one they found entirely invaded They considered it a terminal phase of pneumonia They did not however, use the term massive collapse to describe the condition

Although at that time the condition was considered to be extremely rare, it was beginning to receive more attention Various ideas were offered to explain the cause of its existence Handicapped as these workers in this field then were by lack of modern means of study, it is interesting to note that some of their opinions are closely in accord with modern ideas Gairdener, a young pathologist at the University of Edinburgh, began in 1850 and over a period of three or four years wrote a series of papers in which he related a very thorough account of his studies of collapse of the lung He clearly described obstruction of the bronchus by secretions, being the first to recognize bronchial obstruction as a cause of pulmonary collapse Gairdener also, in his writings, distinguished collapse from pneumonia

From 1908 to 1914, William Pasteur of London published several papers on pulmonary collapse pointing out that it was a frequent post operative complication and that it was not pneumonia as it had usually been diagnosed Pasteur distinguished between lobar and lobular collapse In 1910, he wrote a paper entitled, *Active Lobar Collapse of the Lung after Abdominal Operations*, and as Bowen points out, this paper laid the foundation for the modern conception of the part atelectasis plays in post-operative complications He, at this time, made the first mention of cardiac displacement as a major sign of collapse of the lung

Killian, in 1897, invented the bronchoscope. Bronchoscopy and roentgenology have played the major role in the present day understanding of atelectasis and its clinical manifestations A few years later Jackson improved Killian's original invention, and through the use of this instrument, the Jacksons and their associates have assumed the lead in promoting an understanding of atelectasis

In 1914, Elliot and Dingley, two young London physicians, reported 11 cases of massive collapse. They published the first roentgenograms of pulmonary collapse which definitely demonstrated the displacement of the heart.

Brunn and Brill mention the occurrence of a great many cases of massive collapse during World War I following gun shot wounds of the chest or other chest injuries. These authors mention that Scrimger was the first investigator in this country to use the term postoperative collapse when, in 1921, he reported seven cases occurring in a series of 540 consecutive operations.

In 1925, Jackson called attention to the many similarities in atelectasis produced by foreign bodies and atelectasis following surgical operations. He concluded that they had the same etiology and later in the same year reported the cure of postoperative massive collapse by bronchoscopic aspiration. Since that time there has been an increasing interest in and understanding of atelectasis, particularly that following surgery.

During recent years the term "middle lobe syndrome" has been adopted for designating atelectasis of the middle lobe, with its complications.

At the present time atelectasis occupies an important place in the fields of medicine, surgery and roentgenology—so much so, that it should be thought of as a possibility in all acute and chronic disorders of the lungs. In not a few of these disorders it will be found to be the primary factor.

Classification

In the literature the nomenclature used in the classification of atelectasis varies considerably and there is a lack of uniformity in the terminology in the description of similar conditions where atelectasis exists or has been a factor. The classification of atelectasis, based on origin, may be divided into congenital or acquired; based on etiology into passive or adjustment, compressive and obstructive; and based on extent and distribution into simple and massive.

Congenital Atelectasis

A condition described as congenital atelectasis is failure of the lung or a portion of the lung to expand at birth. There is some controversy among anatomists as to the state of the fetal lung especially of the small bronchi and the alveoli at birth.

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Best and Taylor describe the lungs before birth as containing a small amount of amniotic fluid They say that during that period the thorax is unexpanded and completely filled by the airless lung but that respiratory movement takes place in utero They refer to the work of *Barcroft, Snyder and Rosenfeld* who demonstrated this by injecting india ink into the amniotic sacs of rabbits and finding the ink later in the alveoli

It is felt by Best and Taylor that movement of the amniotic fluid in the lung is a normal event and probably plays an important role in the dilatation of the future air passages They relate that respiratory movements at the rate of 60 per minute have been observed in the human fetus and that these movements have been inhibited by anoxemia or narcotics They believe that with the onset of breathing at birth normally the lung unfolds and greatly increases in size On rare occasions, unfolding of the lungs or of a part of one or both lungs may not take place The result is termed congenital atelectasis The failure to unfold may be due to congenital defects as constriction of the bronchi, absence of alveoli, residual amniotic fluid or the presence of inflammatory products in the bronchi

Acquired Atelectasis

Acquired atelectasis occurs as the result of the tendency of the lung to contract, due to its normal elasticity or as the result of pressure on the surface of the lung or of obstructions of the airways

Passive or Adjustment Atelectasis

As pointed out by Adamson and Dubo, there are certain forces which maintain the lung inflated These are the atmospheric pressure within the lung and the unyielding chest wall Certain factors may reduce the size of the thoracic cavity so as to overcome these forces to the extent that the lung is relaxed but not compressed, the lung then, through its natural contractility, adjusts itself passively to the reduced volume of its containing chamber

The common causes of passive or adjustment atelectasis are fluid or air in the pleural space removal of ribs, paralysis of the diaphragm growths in the chest wall or chest cavity when they produce relaxation rather than compression of the lung

Compression Atelectasis

Compression atelectasis may develop when the reduction in the

volume of the lung is so extensive that it produces compression rather than relaxation Compression atelectasis may be produced by the same factors that produce passive atelectasis

Obstructive Atelectasis

Obstructive atelectasis occurs when the bronchus or bronchi leading to any portion of the lung become occluded so that air cannot enter the alveoli distal to those bronchi and the air remaining in these alveoli is absorbed into the blood Damage to the capillary circulation may interfere with the absorption of the air trapped in the alveoli The cause of obstructive atelectasis may be within the lumen of the bronchus or in the wall of the bronchus when it is said to be intrinsic it may be outside the wall of the bronchus and is then termed extrinsic

Simple Atelectasis

Simple atelectasis is used in the literature at times to describe airlessness of the alveoli when it exists without complications Again it is used to designate atelectasis involving only a portion of a lobe, or a portion of two or more lobes that is, lobular atelectasis It is in this latter sense that the term is used in this chapter

Massive Atelectasis

Massive atelectasis has been used to describe the more extensive involvement of the lung without giving consideration to the lobar divisions of the lung In this discussion, the term is used in referring to involvement of one or more whole lobes or of an entire lung or of both lungs Not infrequently, massive collapse and massive atelectasis are used interchangeably Jackson and his associates have questioned the propriety of using these terms synonymously They feel the term atelectasis, or collapse of the alveolar tissue of the lung, more accurately describes the condition present since, ordinarily, the bronchi are not collapsed

The term true atelectasis, is at times used in the literature in referring to atelectasis where there are apparently no complications present or where the inference is that the condition is reversible It will be used in that sense here

The symptoms, physical and x ray signs, as well as the diagnosis and treatment of atelectasis depend upon its cause, location and extent associated These different factors will be considered as indicated, in discussing atelectasis in connection with the various circumstances

and frequently upon the pulmonary condition with which it may be under which it occurs

The rather wide variation of opinions as to the frequency with which atelectasis occurs under any circumstances may be explained partially by failure to recognize the condition when it is present and partially by difference in terminology

The more common conditions in connection with which atelectasis may develop will be discussed in the following pages

CLINICAL MANIFESTATIONS OF ATELECTASIS

Congenital Atelectasis

Congenital atelectasis is a term commonly used to describe a condition present in the lungs of some babies that are stillborn or that die at birth The atelectasis being widespread in these babies inhibits breathing and causes death At times expension of the lung at birth is not possible due to the absence of alveoli or constriction of the bronchi This is not true atelectasis

In "blue babies," the cyanosis is felt to be caused by relatively minor degrees of simple atelectasis, which either clear up spontaneously or are cleared up by manipulation of the child or, in the more severe cases, by aspiration of mucus or amniotic fluid

Atelectasis in Children

Varying degrees of a condition which has been termed atelectasis have been reported as being present at birth in some infants which did not clear up but which seemed to lose significance as the child grew and the lung expanded In other cases, infection has been reported as developing in atelectasis which was present at birth Opinions differ as to the part these infected atelectatic areas play in producing permanent lung damage

Anspach described a radiological triangular shadow appearing in the base of chest films of children In the study of more than 50 children he found that a shadow occasionally appeared in both bases He described this as a small well defined dense right triangle with the mesial border, or altitude, and the inferior border, or base, indistinguishable from the shadow of the spine and the leaf of the diaphragm, resp ctively The lateral border, or hypotenuse, of the triangle extended from the hilus to a varying point on the diaphragm The heart and diaphragm and other adjacent structures were drawn toward the

involved side In the study of this group of children, all with bronchiectasis, Anspach found that this shadow was present a few hours or a few days after the onset of the first symptoms of the condition, presumably an atelectasis, which eventually developed into bronchiectasis Others have felt that a similar shadow, at least at times, might be caused by spontaneous pneumothorax within moderately thickened pockets of fluid in the mediastinal pleura or within the mediastinal space It was Anspach's opinion that this shadow was usually, if not always, due to basal atelectasis which, by becoming infected, had been the primary cause of the bronchiectasis in these children Tannenberg and Pinner in correlating their clinical [illegible] of bronch[illegible] chiectasi[illegible] result of [illegible] [illegible]us infections of the lungs [illegible]ectasis was always the [illegible] the true nature of this shadow was recognized and early and frequent drainage instituted, the development of bronchiectasis could be avoided

POSTOPERATIVE ATELECTASIS

Frequency of Occurrence and Cause

The most frequent and important manifestation of atelectasis is its occurrence following surgery or injury It is recognized, at the present time, as the most common post operative pulmonary complication following major operations It occurs most often following abdominal surgery particularly surgery of the upper abdomen involving the stomach and gall bladder The consensus generally is that it occurs approximately twice as frequently following operations in the upper as it does following operations in the lower abdomen The reports of the frequency with which atelectasis occurs differ widely, varying from 2 per cent, following operations in the lower abdomen, to as high as 60 per cent following operations in the upper abdomen The majority of reports indicate that it occurs in approximately 10 per cent of upper abdominal surgery

The figures in regard to the frequency of the occurrence of post operative atelectasis depend upon a great many different factors, such as the recognition or failure in recognition of the condition when it is present, the type, the site and duration of the operation, the technique and skill of the surgeon, the technique and skill of the anesthetist, the presence or absence of acute or chronic respiratory infection at the time of operation, the use of morphine or other narcotics

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The most frequent and important manifestation of atelectasis is its occurrence following surgery or injury It is recognized, at the present time, as the most common post operative pulmonary complication following major operations It occurs most often following abdominal surgery particularly surgery of the upper abdomen involving the stomach and gall bladder The consensus generally is that it occurs approximately twice as frequently following operations in the upper as it does following operations in the lower abdomen The reports of the frequency with which atelectasis occurs differ widely, varying from 2 per cent, following operations in the lower abdomen, to as high as 60 per cent following operations in the upper abdomen The majority of reports indicate that it occurs in approximately 10 per cent of upper abdominal surgery

The figures in regard to the frequency of the occurrence of postoperative atelectasis depend upon a great many different factors, such as the recognition or failure in recognition of the condition when it is present, the type, the site and duration of the operation, the technique and skill of the surgeon, the technique and skill of the anesthetist, the presence or absence of acute or chronic respiratory infection at the time of operation, the use of morphine or other narcotics

as well as sedatives that interfere with the action of the normal mechanism that acts to keep the respiratory tract clear, the position of the patient during, as well as after operation, as position may interfere with drainage of the airways, the age and sex of the patient, atelectasis occurring more frequently in elderly persons and more often in men than in women Men are thought to be prone to chronic irritation of the respiratory tract as the result of inhaling smoke or other irritating particles Again, men are abdominal breathers and interference with the action of the diaphragm incident to abdominal surgery, especially surgery in the proximity of the diaphragm, predisposes to a collection of obstructing material in the lower portion of the lungs It has been suggested that women, in general, are more resistant to respiratory infections than men The general condition of the patient plays a part, that is, debilitated persons are more prone to bronchial obstruction following surgery

Many surgeons prefer spinal anesthesia in the belief that its use affords protection against post operative atelectasis and pneumonia *The consensus of investigators in this field is that the type of anesthetic* makes little or no difference in the frequency with which postoperative atelectasis occurs The possible exception to this statement is cyclopropane This drug is known to stimulate the vagus Atelectasis, resulting from bronchial spasm and increased bronchial secretions which *were felt to be the direct result of this drug, has been reported*

The management of the patient following the operation, especially during the first five or six hours, rather than the type of anesthesia is considered to be the most important factor

The common cause of postoperative atelectasis is obstruction of the bronchi by excessive tenacious secretions or mucus Less commonly, blood and pus play a part in the obstructive process

De Takats, Fenn and Jenkinson have, by animal experimentation *correlated with clinical observations, concluded that certain nervous* reflex stimuli produce bronchospasm and increased bronchial secretions These investigators feel that bronchospasm and increased bronchial secretions so produced are sometimes responsible for the development of postoperative and posttraumatic atelectasis Other workers share this belief These men are of the opinion that such nervous reflex stimuli are due to certain factors, the first of which is manipulation of the abdominal viscera, particularly those in the upper abdominal cavity as the stomach, the mesentery and the cystic ducts They

are of the opinion that the reflex stimuli resulting from abdominal surgery may be due in part to insufficient medication with atropine or scopolamine, to too light an anesthesia, or to the position of the patient on the operating table or possibly to parasympathetic action when cyclopropane is used It is felt that perhaps in most cases, the atelectasis is the result of a combination of these factors

The second factor in the production of nervous reflex stimuli is believed to be pulmonary emboli caused by small blood clots or particles of fat Not infrequently pulmonary complications develop following surgery which are presumed to be the result of emboli formed by small blood clots Similar complications occur following injury to long bones even when no anesthetic is used These are felt to be the result of small fat emboli It has been demonstrated that such emboli occurring in the pulmonary vessels do produce bronchial spasm and increased bronchial secretion

The third factor thought to be instrumental in the production of reflex nervous stimuli is injury to the chest wall It was found that changes in the bronchial tree similar to those following pulmonary emboli took place following contusion of the chest wall These changes occurred when there was no penetration of the chest wall but their occurrence was more frequent with the more severe chest wall injuries

In their experimental work, these investigators were able to prevent these nervous reflex stimuli by bilateral section of the vagus and to a considerable extent by large doses of atropine, through the inhibitory effect of this medication on vagus stimuli

Prevention of Postoperative Atelectasis

Postoperative atelectasis is easy to prevent and easy to recognize if the probability of its occurrence is kept in mind The dividing line between treatment and prevention is by no means always clear Often times the same measures serve the two purposes There are certain steps which, when used in the prevention, will often obviate the development of serious atelectasis or its sequelae

The important preventive measures follow *Efforts should be made* to have the respiratory tract free from secretions or other inflammatory products and to avoid, as far as possible, subjecting the patient to medication or any treatment that will interfere with the normal emptying mechanism of the bronchial tree The use of morphine or other opium derivatives before, during or following the operation should

be reduced to a minimum as those drugs seriously interfere with the clearing of the bronchi and strongly predispose to bronchial obstruction

Major surgery, except in emergency, should not be performed on patients who have acute respiratory infection or even a head cold In individuals who have a chronic respiratory infection with increased bronchial secretions, an attempt should be made to free the respiratory tract of these secretions, previous to surgery, by postural drainage or in extreme cases, by bronchoscopic aspiration Where there is a chronic suppurative condition of the lungs, routine bronchoscopic aspiration prior to and following surgery is advised as a precautionary measure Elderly patients should, when feasible, be directed to be up and about at least for a few weeks before undergoing surgical operations At the time of surgery the patient should be protected from drafts and kept warm During the operation it should be kept in mind that secretions in the upper respiratory tract are easily aspirated, especially when the patient is under general anesthesia and has received medication which suppresses the cough reflex Catheter suction, if and when indicated, should be carried out during the operation and the patient's position should be such, if possible, as to favor drainage of the air passages

It is felt that the efficiency of the anesthetist as well as the skill and technique of the surgeon and the postoperative management of the patient are important factors in preventing atelectasis Some prefer to avoid inhalation anesthesia if a skilled anesthetist is not available As a preventive measure, it has been suggested that post anesthetic rooms should be provided where the patient would be under the care of those trained in the handling of patients under the influence of a general anesthetic and who would be in a position to meet emergencies as they arise

It has also been suggested that in closed anesthesia an effort should be made to keep the respiratory tract clear by periodic aspiration and inflation of the lungs by intratracheal pressure Under all conditions the anesthetic should be stopped as soon as circumstances permit In the prevention of atelectasis following surgery, as soon as the operation is finished, every effort should be made to have the patient cough vigorously and breathe deeply During the cough the abdominal wound should be supported, preferably by an attendant as tight binders, especially on the upper part of the abdomen and on

the chest, should be avoided as they interfere with clearing the airways It is also helpful to turn the patient every hour or two to promote pulmonary drainage As soon as the anesthetic is discontinued, the routine flushing of the lungs for several minutes with carbon dioxide 5 to 10 per cent, mixed with oxygen is advocated to stimulate respiration and free the alveoli of the more readily absorbable anesthetic gases and reduce the likelihood of their collapse Some prefer to use a mixture of 20 per cent oxygen and 80 per cent helium for this purpose

To promote pulmonary drainage and particularly to prevent hypostatic congestion, prolonged recumbency should be avoided in all patients and especially in elderly persons Under conditions where there are excessive amounts of bronchial secretions present, serious postoperative pulmonary complications may be eliminated by bronchoscopic aspiration before the patient leaves the operating table

In patients with a respiratory infection who must undergo surgery, a prophylactic course of antibiotic drugs or other indicated medication should be given for a few days before the operation and, at least, for a few days during the postoperative course

Symptoms of Postoperative Atelectasis

If only a small area or areas of atelectasis exist, there are usually no symptoms With an increasing amount of lung tissue affected, the symptoms become increasingly apparent They usually are sudden in onset but in rare cases may develop slowly

Not infrequently, even when there is considerable involvement, the patient experiences only a feeling of tightness or constriction in the base of one lung or it may be only a vague discomfort or oppression which accompanies breathing Again at times, as pointed out by Cecil, the patient sits upright in bed and appears cyanotic, has rapid respiration and an anxious face, but does not have the general appearance of being sick unless he is sick from other causes

On the other hand, occasionally where the symptoms are severe, the patient may be prostrated Severe cough, expectoration, rapid shallow respiration, and tachycardia are present only in the more grossly involved cases The temperature and pulse vary as to the cause and effect The temperature may range from 101°-104° F , the pulse, where the atelectasis is extensive and unilateral, may rise to 120-140 The pulse is usually proportionately more affected because of the shift

of the heart and mediastinum, and for the same reason the pulse, as a rule, returns to normal sooner than the temperature The patient may complain of varying degrees of pain which does not seem to be directly connected with the location of the atelectasis It is thought to be due largely to the pull on the diaphragm and its costal attachments

Physical Signs of Postoperative Atelectasis

The physical signs of postoperative atelectasis most frequently are in the base of the lung If the atelectasis is small usually there are no physical signs Signs become apparent and increasingly manifest with increasing involvement of pulmonary tissue They vary greatly, depending upon the cause as well as upon the type of atelectasis present When the atelectasis is extensive enough to produce signs, the principal ones are suppression of breath and voice sounds Breath sounds may, at times, be absent or bronchial Coarse musical rales distant in character may be heard when the atelectasis is developing or clearing The voice sounds will vary depending upon the degree and extent of the collapse of pulmonary tissue A pleural rub may be audible In atelectasis, impaired percussion or dullness is present for the most part only when a relatively large amount of subpleural lung tissue is affected In lobular atelectasis, the signs may be transient as old areas clear up and new areas develop Change in the position of the patient may cause these signs to vary The percussion note is hyper resonant over the opposite lung as well as over the uninvolved portion of the lung on the affected side when compensatory emphysema is present

In lobar atelectasis involving the base of the lung, if the involvement is on the left side, there is a triangular area of dullness, posterior to the heart If the involvement is on the right there is a triangular dullness in the corresponding area on the right Elevation of the liver may account for a flat percussion note on the right If the right middle lobe is involved, the signs are usually elicited over the lower third of the anterior right chest It should be remembered that following abdominal surgery, due to pain and soreness, there may be limited breathing, especially in the lower part of the lungs, and there may be certain changes in the voice, breath and percussion sounds as well as some indefinite rales in the absence of demonstrable atelectasis

Radiological Signs of Postoperative Atelectasis

Since the lower portions of the lungs are more frequently involved there is usually a basal opacity Opacities however, may appear in other parts of the lungs When the atelectasis is of the lobular type, roentgenograms may show irregular patchy areas of varying size and distribution resembling the appearance of bronchopneumonia If the atelectatic area is small it may have a lenticular appearance The classical x ray appearance of atelectasis particularly of the massive type or where the condition has an extensive unilateral distribution, is a shift of the heart and other mediastinal structures toward the involved side with a rise of the diaphragm and diminished motion or fixation of the chest wall on the same side These 'indrawn signs are the result of the negative pressure in the hemithorax incident to the atelec tasis Depression of the intercostal spaces or flatness of the chest wall as a rule, are not present when the atelectasis is of recent occurrence The degree of negative pressure which develops in the throacic cavity is dependent upon the mobility of the mediastinum There is usually evidence of emphysema in the unaffected lung or in the uninvolved portion of the affected lung

Robins and Hale in a study of six hundred cases of massive col lapse occurring postoperatively in the Massachusetts General Hospi tal found that one lobe was involved in 71 per cent, two lobes in 18 per cent, and three lobes in 11 per cent In this same series they found atelectasis in the left lower lobe in 42 per cent, in the right lower lobe in 26 per cent in the right middle lobe in 26 per cent, in the left upper lobe in 8 per cent and in the right upper lobe in 8 per cent

Fleischner, *et al*, described the radiological appearance of a linear or plate like atelectasis This shadow is usually in the base of the lungs just above the diaphragm The atelectasis is believed to be the result of the obstruction of the finer bronchi and caused by conditions that tend to decrease the respiratory movement in the lower chest These conditions are pain and soreness due to pleurisy or injury to the chest wall or inflammation or soreness in the subphrenic region or upper abdomen

Radiologically, these linear shadows may be confused with shad ows produced by the healing stage of infarcts, by interlobar effusion or less frequently by the occlusion of pulmonary vessels by metastasis

These plate like atelectatic shadows are usually long traversing the entire lung and they always stop at the interlobar fissure. They may be multiple and may occur in different, but as a rule, horizontal planes. Occasionally, the shadow may appear oblique. These shadows may be barely visible or they may be 5 or 6 mm wide. They have a well defined border and there is usually evidence of emphysema on each side of the shadow. With few exceptions they disappear in a few days.

Atelectasis and Pulmonary Tuberculosis

During the course of pulmonary tuberculosis, atelectasis is a relatively common occurrence. In this disease, there are many factors predisposing to bronchial obstruction. These are inflammatory secretions and caseous material in the bronchi, constriction of the bronchi as the result of endobronchial tuberculosis and fibrosis, during collapse therapy compression of the pulmonary tissue as a whole, and pressure of enlarged lymphatic nodes and tuberculomata. A combination of some or of all of these factors may serve to produce airlessness of the alveoli. Kent pointed out that the so-called epituberculosis is in reality an atelectasis resulting from bronchial occlusion and that it may at times involve a part of a lobe or one or more lobes or a whole lung.

Atelectasis occurring in connection with pulmonary tuberculosis is perhaps most frequently not recognized as such because it remains true atelectasis for only a short period.

Pinner, in the pathological study of tuberculous lungs, found uncomplicated atelectasis to be exceedingly rare. His explanation of this was that pneumonic processes are prone to develop in these cases with the onset of impairment of bronchial drainage. Microscopically, his findings were for the most part those of a tuberculous pneumonia, rarely a non tuberculous pneumonia. He stressed the fact that tuberculous pneumonia may have a very acute onset and is not infrequently considered to be atelectasis.

Vorwald and Adams, as the result of experimental study, described the influence of atelectasis following bronchial obstruction in the closure of cavities and the control of tuberculosis distal to the occlusion. Apparently here, the term atelectasis was used to include not only airlessness of the pulmonary tissue but also the chain of conditions which ensued and resulted in prolonged or permanent decrease

of the lung volume Atelectasis was perhaps the initiating factor but did not continue to exist as such These investigators emphasized that the greater the duration of the bronchial obstruction, the more favorable was the effect on the tuberculosis

Atelectasis and Pneumothorax

Atelectasis occurs frequently in connection with pneumothorax therapy It may be of the adjustment, compressive or of the obstructive type The symptoms and signs will vary with the type and extent of the involvement Usually, the roentgenological signs are the most obvious and the most informative

When the atelectasis is due to the obstruction of a primary bronchus and occurs suddenly, the absorption of the air in the alveoli distal to the obstruction, where the capillary blood supply of the bronchi has not been previously damaged, takes place rapidly, usually in the course of a few hours If the involved portion of the lung has been previously free of disease, roentgenologically it will appear as a small dense shadow In human beings, the volume of the completely airless lung is 1/3 or less than that of the volume of the normally inflated lung When the obstruction occurs in a primary bronchus in which an inflammatory process already exists, or if infection and pneumonitis develop coincident with or relatively soon following obstruction, the collapse of the involved portion of the lung parenchyma is not so marked The roentgenogram, under this condition, has the "ground glass" or homogeneous appearance Again, where the atelectasis is extensive, producing a marked intrapulmonary and intrapleural negative pressure, fluid tends to be drawn out of the blood and lymph vessels into the lung tissue causing what has been termed the drowned lung' which casts an opaque or homogeneous shadow on the roentgenogram

At times, where the bronchial obstruction is not complete but interferes with drainage of the airways to the extent that secretions are retained and only certain degrees of infection and inflammatory reaction develop, the lung distal to the obstruction may have a less opaque homogeneous appearance in contrast to the normal portion of the lung, which, although partially collapsed, is still roentgenologically translucent

Bronchial obstruction and atelectasis with its sequelae, occurring in connection with pneumothorax therapy or pulmonary tuberculosis,

may have a very serious significance, as the lung or the involved portion of the lung may fail to *reexpand and be permanently crippled* This condition also at times predisposes to the development of empyema *With the present very efficient* development of other forms of mechanical therapy, as well as the more accurate knowledge and understanding in the selection of patients suitable for pneumothorax treatment, tuberculous patients in whom tension cavities indicate bronchial obstruction or in whom bronchoscopy reveals the presence of tuberculous lesions in the bronchial walls are as a rule now regarded as unsatisfactory for pneumothorax therapy If for any reason it is deemed expedient to institute pneumothorax in patients with these types of involvement they should be placed on a strict rest regimen and antibiotic therapy, at least *for a period, before pneumothorax* is established It is possible by this course in some cases to clear up specific *lesions in the lumen of the bronchi so as to obviate bronchial obstruction* if and when pneumothorax is instituted

When atelectasis occurs in connection with pneumothorax, except where it involves a limited area with cavity closure, effort should be made to correct the condition In the rare cases where the bronchial obstruction is due to a mucous plug, the atelectasis may be cleared up by bronchoscopic aspiration It is usually expedient, however, under these conditions to abandon the pneumothorax either partially or completely

Atelectasis and Pneumoperitoneum

An occasional case of massive atelectasis has been reported as occurring in connection with pneumoperitoneum in the treatment of pulmonary tuberculosis The mechanism involved in the development of atelectasis in the presence of pneumoperitoneum is similar to that involved in the development of atelectasis in the course of pneumothorax therapy There is, however, in pneumoperitoneum, less likelihood of the occurrence of atelectasis of a serious nature

Atelectasis and Thoracoplasty

Davison feels that atelectasis is the most frequent pulmonary complication of thoracoplasty It may occur on the side of the operation or in the contralateral lung It occurs most commonly in the lower lobe of the operated side, particularly so if the diaphragm on that side has been previously paralyzed by phrenic interruption The usual cause of the atelectasis is obstruction of the bronchi by excessive secre

tions The presence of tracheobronchial tuberculosis, especially if it has produced some degree of stenosis, increases the frequency of the development of bronchial obstruction and atelectasis Occlusion of the larger bronchi, the walls of which are more or less rigid and are not compressed by the usual pressure of induced pneumothorax may be brought about by the greater pressure incident to thoracoplasty

The treatment of atelectasis subsequent to thoracoplasty is essentially the same as that discussed in connection with the treatment of postoperative atelectasis

Atelectasis and Marked Pressure in the Pleural Cavity

Hydrothorax, or blood or pus in the pleural cavity as well as spontaneous pneumothorax may, by the excessive pressure exerted on the peripheral surface of the lung produce atelectasis in the lung on the affected side similar to the manner in which it is produced by thoracoplasty

Atelectasis and Pulmonary Hemorrhage

Atelectasis is a hazard of pulmonary hemorrhage occurring from any cause It occurs primarily as the result of occlusion of the bronchi by blood clots

Serious atelectasis occurring in connection with pulmonary hemorrhage is as a rule, the result of treatment rather than of the hemorrhage It is commonly considered posthemorrhagic pneumonia It occurs for the most part, in those patients where morphine or other cough suppressing drugs are administered Such medication is contraindicated as it has a likelihood of doing much more harm than good in the treatment of the hemorrhage

Occasionally in pulmonary tuberculosis or other destructive conditions of the lung there may be slow oozing of blood If the patient is lying quietly or asleep this blood may collect in the upper part of the bronchial tree in the form of a large clot This clot may be suddenly aspirated into a large bronchus and produce very sudden and severe atelectasis Immediate catheter or bronchoscopic suction, preferably the latter, and the administration of oxygen should be instituted and may be life saving

Atelectasis and Influenza

It is felt that atelectasis, perhaps more commonly of the lobular type, is a frequent occurrence in patients with influenza The trans

mural or collateral respiration between the alveoli of the lobar segments is believed to play a prominent part in preventing the more frequent occurrence of serious atelectasis or collapse in patients with influenza The presence of atelectasis occurring in these cases often results in considerable confusion in regard to symptoms, physical and roentgenological findings and diagnosis

Atelectasis and Pneumonia

Cecil says that, on fluoroscopic inspection or study of x ray pictures of the chests of patients with pneumonia, at times one or more lobes are found to be atelectatic with the characteristic "indrawn" signs In these conditions, apparently atelectasis is playing or has played an important part in the pulmonary process Cecil feels that if atelectasis occurs during or coincident with pneumonia it has a serious significance It may not only make recovery more uncertain but may result in, at least, some degree of permanent lung damage If it occurs after the pneumonia has run its course, which is usually what takes place, the atelectasis merely prolongs the convalescence and reexpansion takes place *In general, there is no special treatment indicated* The atelectasis is presumed to be the result of bronchial occlusion with tenacious secretions and mucus Removal of this obstructing plug, occasionally *may afford dramatic relief*

Some go so far as to believe that acute pneumonia is mainly an obstructive process and have advocated bronchoscopic aspiration as treatment Yater has seen massive collapse occur occasionally just preceding consolidation in pneumonia where the signs were those of atelectasis and the symptoms were those of pneumonia

In the virus pneumonias, circumscribed areas of atelectasis occur not uncommonly but are not easily detected The involvement of the small bronchi produce patchy areas of atelectatic lung which are not easy to differentiate on roentgenograms or otherwise from bronchopneumonic consolidations Where the patient is actually sick with fever, not infrequently both conditions may exist

Atelectasis and Pertussis

Atelectasis is considered to be a common complication of pertussis due to the temporary plugging of the bronchi with excessive secretions and mucus It is usually interpreted as pneumonia When treatment is required, the usual steps for relieving this type of bronchial obstruction should be employed

Atelectasis and Paralysis of the Respiratory Muscles

Atelectasis is a frequent and serious complication in patients with respiratory difficulties that result from paralysis or interference with the action of the diaphragm or intercostal muscles Such a condition may obtain in poliomyelitis, diphtheria and certain lesions of the central nervous system These patients are unable to cough and clear the airways, and secretions tend to collect in the bronchi, producing obstruction

Since the general condition of these patients, as a rule, is below par, there is always strong likelihood that the interference with the bronchial drainage will be followed by infection and pneumonia Preventive measures are important These individuals should be protected from contact with those who have acute colds or respiratory infections and if any evidence of respiratory infection develops, they should receive antibiotic drugs and other of the simpler therapeutic measures such as tracheal suction Prompt institution of tracheotomy may be a life saving measure in severe respiratory distress with inability to clear the respiratory tract such as may occur as complication of poliomyelitis, injuries to the head or chest, neurological procedures or other acute laryngeal obstructions If relief is not prompt, bronchoscopic aspiration should be instituted

Atelectasis and Asthma

Atelectasis is doubtless present to some extent in connection with asthma much more frequently than it is detected Cole and his associates reported four cases of massive atelectasis occurring associated with asthma It was their feeling that atelectasis was more common in women than in men and children The most common factors in the production of atelectasis in asthmatics are the chronic inflammatory products in the bronchi and spasm of the bronchial musculature, all of which no doubt play a part in the bronchial obstruction

Allergic individuals, as a whole, are perhaps more prone to develop atelectasis as there is a greater tendency in these cases to swelling and edema of the mucous membrane of the bronchial tree and spasm of the musculature

Atelectasis and Neoplastic Growths or Foreign Bodies

Less frequent causes of bronchial obstruction which result in atelectasis are benign or malignant tumors, enlarged lymph nodes, aneurysms, cysts and foreign bodies In foreign body obstruction where

complete intrinsic or extrinsic bronchial obstruction in rabbits may exist for several months without complications provided the lung does not become infected However, bronchial obstruction in man is prone to relatively early infection as the secretions distal to the obstruction are rarely sterile When relief is not accomplished by the more conservative methods mechanical aspiration through an intratracheally placed catheter or through the bronchoscope should be instituted within a period not to exceed 12 hours Catheter aspiration, requiring the more simple equipment and being as a rule the more easily carried out, should be instituted

Several different techniques for catheter aspiration have been used The catheter has been inserted into the trachea either through the nasal passage or through the oral cavity Passing the catheter through the nasal passage and attempting to insert it blindly into the trachea is a procedure which can be easily learned and effectively applied Insertion of the catheter into the trachea by means of an anesthetist s laryngoscope may be accomplished when blind technique fails Suction is most effectively applied with the use of a glass Y adapter placed between the catheter and the suction machine tube permitting intermittent control of the suction by the thumb This technique prevents severe dyspnea and collapse of the lungs If a Y adapter is not available the cathether should be introduced into the trachea with the suction machine turned off to prevent the catheter from adhering to the mucous membranes With the use of the Y adapter introduction of the catheter is further facilitated if the noise of the suction machine is eliminated by having the machine turned off, making it possible to hear the breath sounds through the open arm of the 'Y adapter

Waters describes a technique designed to avoid the hazard of the vocal cords closing spasmodically on the intratracheal catheter and preventing the entrance of air from without, as the negative pressure produced might cause collapse of both lungs In this technique, intubation of the trachea is done as a preliminary step The tube used for intubation is slightly larger than the suction catheter and preferably is somewhat more rigid The intubation is ordinarily done through the oral cavity but is sometimes carried out through the nasal passage The suction catheter is then passed in its full length through this tube into the trachea Sizes 14 18 French urethral catheters 30 cm long are used for suction purposes

Catheter suction obviously requires that some one be at hand who

through training and experience, is able to carry out the procedure with efficiency Few physicians in the past however, other than anesthetists have had the experience that enabled them to perform catheter suction Since it is now recognized that bronchial obstruction by tenacious secretions mucus and other liquid material is the major factor in post-operative pulmonary complications a training in the technique of catheter suction should be a part of the equipment of all those including nurses who have the responsibility of the postoperative care of the patient

If catheter suction fails or cannot be instituted, bronchoscopic aspiration should be performed Usually the more desperate the condition of the patient the more imperative it is that the bronchoscopic aspiration should be established In bronchoscopic aspiration the operator has the advantage of being able to work by direct vision He is able to study the lumen of the bronchus as well as the mucous membrane and to obtain information about the secretions or other obstructing matter If a large bronchus is obstructed the obstruction can usually be located and obstructing material such as foreign bodies impacted secretions and other inflammatory products can be directly removed When the obstruction is beyond the vision of the bronchoscope it is possible to instill medication such as adrenalin or adrenalin mixtures into the bronchus or bronchi tributary to the atelectatic portion of the lung Such medication usually contributes in a major degree to alleviating the condition This medication together with the cough induced by bronchoscopy frequently relieves the condition

The cough resulting from the stimulation of the cough reflex by catheter suction or bronchoscopic aspiration plays a prominent part in all cases in dislodging the tenacious secretions and mucopus which occlude the bronchi When purulent pulmonary infections are present repeated bronchoscopic suction is usually indicated In all cases of atelectasis even after the evacuation of secretions or inflammatory products or other obstructing material antibiotic drugs should be routinely given orally parentally and/or as aerosols since usually varying degrees of infection are already present in the bronchial tree or will shortly develop in the absence of prophylactic measures

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insufficiency Educating the handicapped patient with pulmonary fibrosis may bring about for him reasonable physical comfort and content ment It may not be amiss to say at this time that one is obligated to salvage a respiratory cripple just as much as one has been doing it with cardiac cripples

The second important therapeutic intervention is directed toward coping with coexistent parenchymal and bronchial infections Measures discussed in the respective chapters are followed in the management of such conditions We have found carbon dioxide given by inhalations the most efficient expectorant The inhalations are given from a cylinder which contains a mixture of 5 per cent carbon dioxide and 95 per cent oxygen A reducing valve and a flow meter are attached to the cylinder Inhalations are best given through a BLB oronasal mask three times a day, with a flow of the gas mixture 5 liters per minute, for a period of 10 to 15 minutes each time More than 20 years' experience with this treatment has proved that it is a safe procedure that can be continued for several months if necessary The frequency and length of inhalations are arranged according to the individual requirements of the case

It has been pointed out previously that reflex bronchial and bronchiolar spasm contributes to the patient s dyspnea in no small manner It is well to place special emphasis on the concept that spasm of the smooth muscles of the bronchi and bronchioles is but the painless colic of the lower respiratory tract Painless though it is, its serious implications make it mandatory to give to it as much therapeutic atten tion as to renal colic or biliary colic Adequate doses of aminophylline ephedrine hydrochloride and related drugs are of paramount importance in this regard Richards and his associates observed alleviation of cough, relief from dyspnea, increase in the vital capacity and in the maximum breathing capacity after periodic inhalation of a one per cent solution of neosynephrine One cubic centimeter of this solution is placed in a vaporizer and aerosolized with a 4 to 7 liter per minute flow of oxygen from a pressure tank which is provided with a reducing valve and flow meter The nozzle of the vaporizer is held in the oropharynx One cubic centimeter of the solution is vaporized in from three to ten minutes Inhalations are given four times a day at intervals most helpful to the patient Neosynephrine administered in this form has no side effects even when it is used for an extended period of time

Complicating emphysema is treated along the lines given in the respective chapter Our experience with artificial pnumoperitoneum

has been highly satisfactory in these cases Barach, and subsequently a number of other clinicians noted satisfactory symptomatic relief from the inhalation of a mixture of 20 to 35 per cent oxygen and 65 to 80 per cent helium Inhalations are given through a face mask, with a flow of 4 to 5 liters per minute or in a helium proof tent The selection of the method of administration depends upon the patient s condition

Failure of the right ventricle is treated with one of the digitalis alkaloids or with strophantin Whenever indicated diuretics are given in the form of combined xanthines and mercurials and appropriate arrangements are made for special diet low in sodium chloride. We have found Neocurtasal (Winthrop) an excellent salt substitute Provisions should be made to cover normal vitamin requirements

A unique method was introduced recently by Harte (1945 to 1946) for the surgical treatment of certain forms of pulmonary fibrosis A patient of his developed severe chest pain following postoperative pulmonary infarction The pain was exasperating and persisted for a period of three and one half months after operation Roentgenologic examination revealed a moderately dense shadow occupying an area corresponding to the right lower lobe This was interpreted as representing thickening and extensive adhesion of the visceral pleura to the chest wall For this reason surgical intervention was recommended for the severance of these adhesions in anticipation that the continuous tug exerted by the pleural symphysis would be eliminated The operation was followed by complete relief from chest pain In addition to symptomatic well being of the patient follow up examinations revealed the disappearance of the x ray shadow from over the right lower lobe

Acute diffuse interstitial pulmonary fibrosis is a newly recognized clinical entity Hamman and Rich called attention to this peculiar clinical syndrome in 1933 and 1935 They summarized the characteristic pathologic findings as follows

(1) It is an inflammatory process with edema hemorrhage and few leucocytes which is different from ordinary pneumonia of bacterial origin

(2) There is an enlargement of the lining alveolar cells

(3) Necrosis of the alveolar and bronchial epithelium

(4) Formation of a hyaline membrane that lines the alveoli

5(6) Extensive diffuse and progressive interstitial proliferation of fibrous tissue throughout all lobes of both lungs associated with focal organization of intra alveolar hemorrhage.

insufficiency Educating the handicapped patient with pulmonary fibrosis may bring about for him reasonable physical comfort and contentment It may not be amiss to say at this time that one is obligated to salvage a respiratory cripple just as much as one has been doing it with cardiac cripples

The second important therapeutic intervention is directed toward coping with coexistent parenchymal and bronchial infections Measures discussed in the respective chapters are followed in the management of such conditions We have found carbon dioxide given by inhalations the most efficient expectorant The inhalations are given from a cylinder which contains a mixture of 5 per cent carbon dioxide and 95 per cent oxygen A reducing valve and a flow meter are attached to the cylinder Inhalations are best given through a BLB oronasal mask three times a day with a flow of the gas mixture 5 liters per minute for a period of 10 to 15 minutes each time More than 20 years' experience with this treatment has proved that it is a safe procedure that can be continued for several months if necessary The frequency and length of inhalations are arranged according to the individual requirements of the case

It has been pointed out previously that reflex bronchial and bronchiolar spasm contributes to the patient s dyspnea in no small manner It is well to place special emphasis on the concept that spasm of the smooth muscles of the bronchi and bronchioles is but the painless colic of the lower respiratory tract Painless though it is, its serious implications make it mandatory to give to it as much therapeutic attention as to renal colic or biliary colic Adequate doses of aminophylline ephedrine hydrochloride and related drugs are of paramount importance in this regard Richards and his associates observed alleviation of cough relief from dyspnea, increase in the vital capacity and in the maximum breathing capacity after periodic inhalation of a one per cent solution of neosynephrine One cubic centimeter of this solution is placed in a vaporizer and aerosolized with a 4 to 7 liter per minute flow of oxygen from a pressure tank which is provided with a reducing valve and flow meter The nozzle of the vaporizer is held in the oropharynx One cubic centimeter of the solution is vaporized in from three to ten minutes Inhalations are given four times a day at intervals most helpful to the patient Neosynephrine administered in this form has no side-effects even when it is used for an extended period of time

Complicating emphysema is treated along the lines given in the respective chapter Our experience with artificial pnumopentoneum

has been highly satisfactory in these cases Barach, and subsequently a number of other clinicians, noted satisfactory symptomatic relief from the inhalation of a mixture of 20 to 35 per cent oxygen and 65 to 80 per cent helium Inhalations are given through a face mask, with a flow of 4 to 5 liters per minute or in a helium proof tent The selection of the method of administration depends upon the patient s condition

Failure of the right ventricle is treated with one of the digitalis alkaloids or with strophantin Whenever indicated diuretics are given in the form of combined xanthines and mercurials and appropriate arrangements are made for special diet low in sodium chloride We have found Neocurtasal (Winthrop) an excellent salt substitute Provisions should be made to cover normal vitamin requirements

A unique method was introduced recently by Harte (1945 to 1946) for the surgical treatment of certain forms of pulmonary fibrosis A patient of his developed severe chest pain following postoperative pulmonary infarction The pain was exasperating and persisted for a period of three and one half months after operation Roentgenologic examination revealed a moderately dense shadow occupying an area corresponding to the right lower lobe This was interpreted as representing thickening and extensive adhesion of the visceral pleura to the chest wall For this reason, surgical intervention was recommended for the severance of these adhesions in anticipation that the continuous tug exerted by the pleural symphisis would be eliminated The operation was followed by complete relief from chest pain In addition to symptomatic well being of the patient, follow up examinations revealed the disappearance of the x ray shadow from over the right lower lobe

Acute diffuse interstitial pulmonary fibrosis is a newly recognized clinical entity Hamman and Rich called attention to this peculiar clinical syndrome in 1933 and 1935 They summarized the characteristic pathologic findings as follows

(1) It is an inflammatory process, with edema, hemorrhage and few leucocytes, which is different from ordinary pneumonia of bacterial origin

(2) There is an enlargement of the lining alveolar cells

(3) Necrosis of the alveolar and bronchial epithelium

(4) Formation of a hyaline membrane that lines the alveoli

(6) Extensive, diffuse and progressive interstitial proliferation of fibrous tissue throughout all lobes of both lungs, associated with focal organization of intra alveolar hemorrhage

(7) Eosinophilic leucocytes in the interstitial tissue in three out of four cases

(8) There are no stainable bacteria *in the lesions* *Identical* *observations* were made by Doenecke (1931) and Belt (1931) in Germany in a chemist who died of an illness of two and a half years' duration after a two-year exposure to radium emanations Eder and his associates and Potter and Gerber reported additional cases

With the exception of one patient, *the onset of the disease is reported* as insidious It ensues with symptoms suggestive of a "common cold or with malaise, dyspnea and cough Dyspnea is first noted on exertion but in few weeks it persists even when the patient stays in bed As a matter of fact, dyspnea gradually but rapidly grows worse and may be present whether the patient is lying flat or sitting up in bed. In one patient, the onset was acute with severe chest pain In another, shaking chills were observed late in the disease With the progress of the disease cough becomes brassy, harrassing and changes from unproductive to productive of small amounts of yellowish or greenish tenacious, occasionally blood streaked mucoid sputum When chest pain is complained of it is more severe on deep inspiration Toward the end of the disease, dyspnea becomes extremely severe, with panting respirations, there are signs of marked exhaustion, prostration and the patient may become delirious

On physical examination cyanosis is obvious *It becomes very intense* in the late stages of the disease Cyanosis is explained on the basis of loss of free alveolar surface, reduction of blood flow in the branches of the pulmonary artery, decreased elasticity of the lung and the development of pleural adhesions which fix the lung to the chest wall In consequence *of these pathologic alterations, there is a marked* decrease in the functional capacity of the so called alveolar capillary gear and in the mechanical competency of the lung as a whole

There is no fever or only a slight elevation of the temperature with the onset of the disease During the early phase, it varies from normal to 100° F Later, it may reach 103°, only to subside subsequently, with occasional, irregular rises to subfebrile levels

The respiratory excursions of the chest are restricted Physical findings are less than one would expect in relation to the dyspnea and cyanosis Impaired percussion *note or dullness is found at the base* or lower one half of the lung on one or both sides The breath sounds are harsh and prolonged and there are fine or coarse moist rales over the areas of changed percussion note Subsequently, numerous moist rales

become audible throughout both lungs, although more pronounced over the basal regions Also, pleural friction sound may be detected over the lateral aspects of the chest or near the heart Late in the course of the disease, the cardiac dullness is found to be enlarged, the veins of the neck are engorged, the liver becomes palpable below the costal margin, there is pitting edema of the legs with generalized anasarca and possibly pleural effusion and ascites The latter, in one case, showed the characteristics of a transudate In another patient the pleural effusion was straw-colored, turbid and contained 900 cells per cubic millimeter, of these 60 per cent were erythrocytes and 40 per cent leucocytes Of the leucocytes, 90 per cent were mononuclear cells and 10 per cent polymorphonuclears

Roentgenograms of the chest reveal extensive fine mottling like that seen in miliary tuberculosis throughout both lungs or large areas of bronchopneumonic consolidation Also, one finds signs suggestive of pulmonary edema and possibly, slight pleural thickening or pleural effusion Teleroentgenogram shows an enlargement of the right side of the heart Interestingly, cor pulmonale develops in from three to four weeks in consequence of the rapidly advancing extensive fibrosis which obliterates the pulmonary capillary bed

Laboratory examinations do not offer positive clues as to the etiology of this disease Blood cultures are negative for pathogenic microorganisms Sputum specimens do not contain bacterial flora which could be considered responsible for this condition Specific complement fixation tests and agglutination tests with the blood serum are negative for bacterial rickettsial and viral infections There is a slight or moderate leucocytosis but late in the disease white blood cell counts have been recorded as high as 55 000 per cubic millimeter The oxygen content of the blood is greatly reduced The arm to-tongue circulation time is prolonged Electrocardiograms show a definite right axis deviation

In establishing the diagnosis, it is mandatory to rule out conditions the clinical picture or roentgenologic findings of which may resemble this disease In addition to diseases that are recognizable with the aid of the aforementioned specific tests one should exclude those which cast widespread miliary nodular shadows on the roentgenogram These include miliary abscesses, certain forms of pulmonary amyloidosis, miliary bronchopneumonias, diffuse bronchiolitis, Bouillaud s disease, metastatic carcinoma congenital miliary form of cystic disease of the lung fungus infection Hodgkin s disease, pulmonary changes secondary

to hemorrhage, lymphatic leukemia, lupus erythematosus melioidosis periarteritis nodosa, *hemorrhagic purpura*, schistosomiasis, acute silicosis, miliary gummas, miliary tuberculosis, tropical eosinophilia and virus pneumonia

The prognosis is hopeless All patients reported so far, died There are variations in the course of the disease which *may create false hopes* as to recovery Substantial transient recession of fever and clearing of some of the physical findings have been observed together with temporary improvements in the subjective feeling of the patient. But after a course which may last from one and a half to six months, fatal termination inevitably ensues due either to heart failure or respiratory failure

It is evident that therapeutic measures are limited to palliative and symptomatic interventions Administration of oxygen in a tent or through nasal catheter is bound to bring about some relief from the distressing dyspnea and concomitantly, of cyanosis Also, prescribing aminophyllin, for intravenous administration or to be taken orally, morphine or papaverine may be of value in alleviating the symptoms

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Incidence

The present incidence of clinical dust disease is not known Figures are available on the number of workers potentially exposed to dust hazard as of the year 1940 (Public Health Bulletin No 259) and are quoted in the following table

Type of Dust	*No of Workers Exposed*
Silica dust	1,140,000
Coal and Silica Dust	639,000
Silicate dusts	1,433,000
Metal dusts	2,254,000
Non siliceous dusts	923,000
Total	6,389,000

The working population of the U S having increased from 50 million (1940) to over 60 million (1948), the number of exposed workers is now over 6 million

On the basis of data gleaned from numerous reports in the literature of the past 20 years, it is possible to form an approximate estimate of the incidence of clinical pneumoconiosis in the above listed dust hazard industries Siliceous dust — 25 to 30 per cent Mixed dusts — 15 to 20 per cent Silicate dust — 10 to 12 percent Metals — 3 to 5 per cent Non siliceous dusts 1 per cent and less Estimating on the basis of the above figures, the incidence of clinical dust disease in this country is between one half to one million cases

It should be remembered however that the above quoted list does not include the beryllium and bauxite industries, the severe hazards of which have been discovered only recently The possibility of others yet to be discovered should also be remembered at this point

However, for the time being, it is still true that silicosis constitutes by far the bulk of clinical dust diseases

General Considerations

Ours is a dust laden atmosphere Even the clean country air is far from dust free Inhalation of dust is a normally unavoidable living condition The human race has evolved under such conditions and our bodies have developed the means of protecting the lungs against inhalation of dust particles to a very large extent Indeed the natural provisions for elimination of inhaled dust particles are ample enough to prevent abnormal dust accumulation in the lungs

CHAPTER XVI

INDUSTRIAL DISEASES OF THE LUNG

THE PNEUMOCONIOSES

By EDGAR MAYER, M D and ISRAEL RAPPAPORT, M D

Introduction

THE EXISTENCE of occupational diseases of the lungs was undoubtedly known to physicians of ancient times, as far back as Pliny, the elder They were described four centuries ago by *Agricola (1550)*, and Ramazzini published an extensive treatise on the subject in 1703 *Zenker coined the term pneumoconiosis*, which has since then been used in a collective sense to include such forms as anthracosis, siderosis, etc, in fact it now signifies any storage of dust in the lungs, even if not a clinical disease The term chalicosis was first used to designate stone-cutters lungs and this was later changed to silicosis Although silica particles *were recovered chemically from the lungs of miners in 1875, it was not* until the early years of 1900 that the real role of silicosis among industrial dust diseases was *revealed It was only in 1922 that Gye and Kettle* demonstrated for the first time that free silica was responsible for the fibrogenic reaction to dust in the lungs

Our modern concepts of the clinical dust diseases have developed only within the last 30 years under the stimulus of progress in industrial *medicine in which occupational dust diseases play an important role* from the medical and medico legal point of view Intensive experimental and clinical studies have been going on simultaneously since then in several centers

However, the problems of dust diseases are as yet far from settled Even while studies on the old questions are still in progress new ones are constantly raised by progress in industrial technics and medical experience *Indeed, only within the last few years new forms of occu*pational dust diseases of the lungs have been revealed the nature of which remains to be settled The whole subject is *still in a state of flux* which will necessarily be reflected in this text

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However for the time being, it is still true that silicosis constitutes by far the bulk of clinical dust diseases

General Considerations

Ours is a dust laden atmosphere Even the clean country air is far from dust free Inhalation of dust is a normally unavoidable living condition The human race has evolved under such conditions and our bodies have developed the means of protecting the lungs against inhalation of dust particles to a very large extent Indeed the natural provisions for elimination of inhaled dust particles are ample enough to prevent abnormal dust accumulation in the lungs

Pneumoconiosis develops only under conditions of exposure to excessive and *prolonged dust inhalation* Even under these conditions pneumoconiosis in form of inert dust storage of embarrassing extent, and especially *in the form of injurious* tissue reaction is relatively unusual The reason for this lies in the vastly differing effects upon the lungs exerted by *various dusts, the greatly* variable conditions under which the industrial dusts are inhaled and the individual s susceptibility, which is *the most variable of all factors*

The development of clinical pneumoconiosis will be easier to understand after consideration of the following factors playing the chief role in its etiology and pathogenesis

(1) The dusts inhaled in industry, their nature and their effects

(2) The functions protecting against accumulation of dust in the lungs

Dust Factors in Pneumoconiosis

Even under conditions of excessive dust concentrations to be found chiefly in industries and upon prolonged occupational exposures relatively few of the exposed workers develop dust disease The main reason for this lies in the fact that very few kinds of dust have the special potency to cause tissue damage and they can exert this effect only under special circumstances These special dust factors will be discussed in the following

From the standpoint of their biological effects dusts can be classified into the following principal groups

(1) *Dusts causing severe and specific forms of fibrosis*

- a Silica (silicosis)
- b Asbestos (asbestosis)
- c Beryllium (beryllıosis) *
- d Bauxite (Shaver s disease)

(2) *Dusts causing modified forms of silicosis or silicatosis* anthracosilicosis siderosilicosis, etc (mixed silicoses) Talcum, mica, etc (mixed silicatoses)

[illegible] this is [illegible] follow [illegible] ucronic [illegible] cosis particles wh ch are now known to play an important role [illegible] In beryllıosis the toxic agent is inhaled into the lungs and exerts its harmful effect at the site where the submicronic part cles are deposited exactly in the manner of other dust conditions The granuloma of beryllıosis and that of s licosis are, as will be shown later, morphologically related somewhat to one another

(3) *Dust causing minimal and nonspecific fibrosis* associated with simple dust storage Anthracosis, Siderosis, Baritosis, etc

(4) *Dusts causing no fibrosis at all*

a Most other inorganic dusts except as follows Dusts of chemical irritants such as acids, alkalis, fluorides, chromates, can cause chemical inflammations in the lungs Some metal fumes such as zinc oxide can cause febrile reactions of unknown nature Dusts of lead arsenic etc , poisons and drugs can cause reactions of systemic poisoning

b *Organic* dusts can cause allergic manifestations or be the carriers of fungi or bacteria Among the former we have asthma from fur, leather, wool, rubber, and other dusts Among the latter we have byssinosis (cotton), bagassosis (cane sugar), tobaccosis, etc

Thus illustrates the fact that few substances present in materials of industry have harmful fibrogenic effect to produce clinical dust disease Indeed, until a few years ago silica in its free state and fibrous silicate of asbestos were the only substances of known fibrogenic power Recently it was discovered that beryllium, a metal is also capable of producing a specific form of fibrosis Still another material of fibrogenic capacity was discovered to be inhaled by processing of bauxite The substances involved in bauxite processing are alumina and silica and possibly some unknown components As was shown above, as far as incidence in industrial medical experience is concerned, these newly discovered forms of pneumoconiosis are negligible as compared with the great practical importance of silicosis asbestosis and the mixed forms of silicoses which constitute by far the largest number of industrial cases Even though the only harmful dust is that containing silica in some form yet great numbers of industries are implicated in hazardous dust exposures This is so because silica in some forms is ubiquitous in nature It makes up the bulk of the earth s crust and is present in all the industries where raw materials from the earth are used All rocks and minerals are intimately associated with silica, hence mining, rock drilling or grinding involve production of siliceous dust There is even enough siliceous dust in the atmosphere outside industrial environment to account for some silicotic fibrosis found in those never exposed to hazardous dust inhalation It is not generally realized that silicotic nodules may even be found in the lung apices and hilar nodes of people not in industry but who have

inhaled siliceous dust in the atmosphere in and about our industrial centers

Practically all harmful dusts contain either silica in its free state (SiO_2) or asbestos, a fibrous hydrated magnesium silicate In free silica, the harmful particles are the crystalline forms of SiO_2 (*quartz, cristobalite, trydimite*) Opal, an amorphous colloidal hydrate as is present in diatomaceous earth, has been found also to have a high fibrogenic capacity now attributed to its content of very fine particles of crystalline* silica *In asbestos, the harmful particles are fibers of fairly large size*

There is a prevailing tendency to identify nodular silicosis with the action of free silica while diffuse fibrosis is considered characteristic of asbestosis and the mixed forms Recent experience — especially since the discovery of newer forms of diffuse fibrosis (diatomaceous earth) — indicates that free silica, of submicronic particle size is responsible for the most severe forms of diffuse fibrosis

The unique fibrogenesis observed in silicosis and asbestosis is still essentially unexplained Silicosis called for a theory based on the chemical action of dissolved very fine free silica particles Now a third theory is called for to explain the effect of diatomaceous earth, namely, that of electronic action by submicronic particles of free silica

The *chemical theory* of the action of silica assumes that very minute particles of silica are readily dissolved in the tissue fluid and the silicic acid so produced acts as a protoplasmic poison This "solubility theory has been difficult to sustain in the light of recent experience The trend now is toward the "surface action" theory which holds that the essential *cause of silicosis is the freshly cloven silica particle* At their freshly fractured surface, these particles carry powerful free and unsatisfied valency *forces avid to take up water and other reactive material* The freshly fractured surfaces of silica particles represent a huge negative ion The *pathologic process consists of hydration of the silica particle* at the expense of the cell protoplasm Because of the atomic lattice structure crystalline silica, when powdered, *yields a more virulent dust than* other silica formations Silica dust is most active as a dry aerosol Heffernan claims hydrosol silica—fully hydrated—*mistakenly called silicic* acid, is nontoxic and enters freely into the metabolism of animals and plants Colloidal silica — partly *hydrated suspension of silica in water* — retains some of the chemical activity of the dry powder, but in a lesser degree All of this explains the *harmless nature of some silica dusts* and the

*Cryptocrystalline

variable noxious effects of others, regardless of their solubility Silica particles exert their harmful effect within the phagocyte As its fractured surface comes in contact with protoplasm silica will hydrate itself at the expense of the fluid content of the protoplasm leading to the death of these cells

Beryllium is the only other substance which has fibrogenic capacity comparable with and often exceeding that of silica As will be shown below, this fibrogenic effect is probably attributable to beryllium oxide the free state of the metal beryllium, while its acid salts are more prone to produce the acute pneumonitic form of berylliosis The reasons for these specific irritating effects of beryllium are yet to be studied

In so called Shaver s disease of workers in bauxite processing plants, it has yet to be determined whether very fine alumina or silica particles inhaled with the fumes emitted from the furnaces at exceedingly high temperatures are the only cause of the severe fibrogenic reaction *

Particle size of inhaled dust plays a predominant role in permitting it to reach and be retained in the airspaces of the lungs The smaller the particles the greater their surface area and the more active they are Dust particles greater than 10 micron hardly reach the alveoli Gardner showed that quartz particles between 3 to 10 microns elicit little if any reaction Those smaller than 3 microns are the active particles In contrast large particles are the definitely harmful factor in asbestosis where fibres of 100 microns are most active Recent experience indicates that as far as the fibrogenic action in silicosis goes there is practically no lower limit of effective size Indeed submicronic silica particles (diatomaceous earth) produce diffuse fibrosis, clinically a far more severe form of pulmonary fibrosis than is discrete nodulation The latter is probably most characteristic of the action of silica particles of micronic size Diffuse fibrosis is also characteristic of asbestosis presumably due to the action of huge fibrous particles of visible size

Particle size of airborne dust is the important factor to be deter

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Velicogna and Evans and Kascht propose that the effect of certain SiO_2 crystals[66] upon phagocyting cells may be explained by piezoelectric activity a property possessed by asymmetric crystals An electric polarity is produced when such a crystal is distorted by pressure Galleyo proposed that the fibrogenic power of SiO_2 crystals is due to ionization effects which may be the manifestation of radioactivity

mined when a question of harmfulness of a dust arises. Recognition now of the submicronic particle size silica retained in tissues is of practical importance X ray diffraction pattern reading has become one of the technical procedures in the diagnosis of silicosis

Concentration of dust refers to the number of particles per unit of air volume (cubic foot) The greater the concentration of irritating dust particles of effective size, the more harmful the exposure, that will result in more rapid and more extensive pulmonary fibrosis There is a safe limit of dust concentration in which men can work without harm even in dusts containing free silica Likewise there is an upper limit beyond which workers will develop pulmonary fibrosis This was so expressed by the National Silicosis Conference "There is evidence that for prolonged exposure a concentration of more than 5 million particles per cubic foot of a highly siliceous dust is dangerous Therefore it is now considered good practice to hold concentrations of highly siliceous dusts at 5 million particles per cubic foot or less'

The limit of concentration differs according to percentage of free silica in the airborne dust In case of mixtures with other particles all of which are essentially inert the harmfulness of the dust will be determined by its free silica content In such cases the limit of permissible concentration is found by multiplying the percentage of free silica by the total dust particle count A dust containing 10 per cent free silica in a total dust concentration of 30 million particles (per cubic foot) amounting to 3 million silica particles is still within the permissible limit There is reason to believe that exposure to very high dust concentrations are harmful even if the free silica content is very low It is considered good practice to prevent concentrations in excess of 50 million particles per cubic foot for even harmless dusts

Dust concentration is a factor also in the *character* of the lesions produced This is indicated by the unusual type of reaction seen in so-called rapid silicosis which develops upon exposure to very pure and fine quartz under conditions favoring excessive concentrations of the dust inhaled

Beryllium appears to be an irritating substance fully active at exceptionally low particle concentration levels While the information on this point is still scant it seems that in beryllium we are dealing with the most irritating of substance known so far In "bauxite fibrosis information is still lacking because the fibrosis producing dust is not yet clearly defined

Dust retention in the lung varies in proportion with the concentration and size particle, and duration of the dust inhaled Determinations of quantity of free and total silica in the lungs of patients dead of pulmonary fibrosis is considered by some of value in establishing the diagnosis of silicosis It has been cited that a content of over 1 per cent of silica of ashed lung is definite evidence that there has been hazardous dust exposure, and this tissue content is usually accompanied by fibrosis Cummings found that in lungs containing less than 1 5 to 2 grams of silica (1 per cent of the weight of dried lung) there usually is no evidence of silicotic reaction The inference is that inhalation of silica is not necessarily productive of silicosis, this occurs only after inhalation of amounts above a minimum, and in a certain duration of exposure which is to be discussed later In berylliosis, also, the beryllium content of lung tissue is considered of value in diagnosis Beryllium in excess of 20 micrograms in 100 grams of dried lung has been found in both acute and chronic berylliosis, and this amount is considered by some as diagnostic of the disease

Duration of exposure As Gardner pointed out it takes time for effective quantities of dust to accumulate within the lungs and more time for the particles to react upon tissues Long periods of exposure are required to produce dust disease In the vast majority of cases the time is measured in years rather than months The average time for development of dust disease under exposure to moderate concentrations of silica particles is 10 to 15 years, and over 25 years for even less irritating dust concentrations The time is proportionately less for higher concentrations of free silica particles Gardner believed two years to be the lowest time limit with the most potent dusts Recent experience indicates that under unusual circumstances the lowest limit is about a year

As to the time element of exposure in berylliosis, information is still too meagre On the one extreme one severe exposure has been alleged to have produced the acute form, while on the other repeated mild exposures are known to lead to chronic berylliosis

Self-cleansing function of the lungs The protection of the respiratory apparatus against excessive dust inhalation begins with the filtering capacity of the nasal passages Lehmann estimated that 50 per cent of dust inhaled is normally trapped in the nasal filters In the air passages dust is prevented from reaching the air spaces The amount of particulate matter in the alveoli is very small, even when the bronchiolar lining is

covered with dust caught in the sieve of mucus spread between the hairs of the dense ciliary brush Most of the dust reaching the interior of the *lungs is precipitated on the* mucosa of the tracheobronchial tree and brought back by the "escalator" movements of the cilia aided by bronchomotor activity

The above two mechanisms bar passage to all the particles larger than 10 micron Only particles below this size reach the alveoli whence they are eliminated by the "self cleansing function" of the lungs employing the cellular as well as humoral mechanisms of defense The stream of fluid which is constantly poured into the alveoli from the capillaries on the arterial side and filtered back on the venous side carries some particles away with the blood stream Others are washed out again into the bronchioles, still others are washed into the lymph stream collected from the alveoli into the lymph radicles Relatively larger particles remaining deposited in the alveolar spaces are engulfed by phagocytes which carry them mostly outward to be eliminated by way of the air passages

The efficiency of the self cleansing function can be appreciated if we recognize that it protects a breathing surface (50 square meters) 20 times that of the skin surface of the body against dust laden air breathed at the rate of 8 liters per minute

Individual Differences

Self cleansing efficiency is a part of the functional capacity of the lungs and as such shows great individual variability Great differences exist between individuals in their ability to handle equal quantities of the same dusts under the same conditions This is probably due to *differences in constitutional lung development* which like other constitutional differences is an inherited quality, influenced by environmental factors affecting body development in general Pneumoconiosis also shows great differences in development in individuals under the same conditions of exposure, probably to be explained by individual variations in self cleansing efficiency

Normal Dust Storage

Self cleansing function of the lungs becomes inadequate in the face of inhalation of amounts of dust in excess of the usual either when dust concentration is too high or when it is inhaled over long periods of time When the dust is inert such failure of self cleansing results in dust storage To some extent such dust storage is normal In our indus

trial environment soot is inhaled throughout life in quantities which lead to physiological anthracosis This is responsible for the characteristic pigmentation of the lungs particularly marked in those living in some industrial sections Coal pigment accumulation in the pulmonary lymphatics, in the regional lymph nodes in the hila and in the subpleural and interstitial lymph spaces increases with age as the quantity of soot retained in the lungs increases

Dust storage in excess of the normal, as will be shown below, is characteristic also of workers in industries who are exposed to excessive concentrations of inert dusts over long periods This leads to the what Gardner called *benign pneumoconiosis* For the most part this does not interfere with normal lung function It is conceivable, however, that dust accumulation may at times reach such proportions as to encroach upon the breathing surface to an embarrassing extent Recent observations indicate that at times even simple anthracosis may become disabling by the extent of emphysema which develops with excessive dust storage leading to disturbed lung function

Self cleansing is a part of intrinsic lung function and depends on intactness of the structures By means of their self cleansing efficiency, whole lobes can clear themselves of a pneumonic infiltration within a few hours However, once the structures have suffered an irreparable injury, self cleansing efficiency is also lost Fibrotic residues of inflammatory lesions in the lungs are first to show retention of coal pigment Klotz showed that in residents of Pittsburgh anthracosis was as marked in individuals with congested lungs as in coal miners

Chronic inflammatory processes in the lungs favor local accumulation of whatever dusts are inhaled In other words, pneumoconiosis is favored by inflammatory lesions in the lungs The reverse, too, is certainly true To a considerable extent pneumoconioses favor local extension of inflammatory processes due to any infection which may be present in the lungs

The natural history of pneumoconiosis is that of *"failure of self cleansing function"* which leaves an indelible record of the dust inhaled during life in characteristic pathologic changes The scene of these changes is the pulmonary lymphatic system, operating with two distinct sets The superficial lymphatics coursing underneath and through the pleura, and the deep lymphatics accompanying the septal interstitium of the vessels and the bronchi everywhere within the lungs The two

sets communicate in the subpleural cortex, permitting lymph drainage toward the surface of the lungs, when drainage towards the roots is impaired Wherever lymphatic trunks communicate, aggregations of lymphoid tissue exist at the distal ends of alveolar ducts, at the bifurcations of blood vessels and bronchi, and at numerous points over the pleural surface About and at the lung roots, large lymph nodes are present to receive the lymph flow and pass it on to the large intrathoracic lymph trunks

In pneumoconiosis, the lymph nodes at the root and the lymphoid tissue knots within the septa and in the cortex of the lung become "depots' of dust laden phagocytes The order of disposition suggests that as dust inhalation continues, stasis from obstructive reaction in the central lymph nodes and vessels (at the roots) shunts the flow of lymph toward the surface of the lungs Thus the first lesions are often produced in the hilar nodes and the pleura

Recent observations indicate that as a rule, dust laden phagocytes migrate from the airspaces by way of the air passages to the vicinity of the lymphoid aggregations situated at the divisions of the respiratory bronchioles Here they pass into the interstitial tissue to enter the lymphatic system As more dust laden phagocytes reach these first lymphoid depots than can be passed on, they become choked with cells Then accumulation of dust cells increases in the airspaces about these 'depots giving the appearance of so many localized focal consolidations within the lung parenchyma

Dust particles are also carried freely in the lymph stream and where this becomes stagnant, these particles are filtered into the surrounding tissues Eventually they accumulate in the interstitium of the lungs particularly in the peripheral perivascular connective tissue sheaths In some forms of "benign pneumoconiosis there may occur here tissue reactions of slight amounts in addition to mere aggregation of dust particles Both of these increase the amount of connective tissue in the delicate peripheral framework of the lungs Thickening of the vascular trunks becomes a demonstrable morphologic and x ray feature Here we are dealing with features bordering on pneumoconiotic fibrosis The transition from benign (simple) pneumoconiosis to true dust fibrosis is not an abrupt one It leads by way of low grade reactions to apparently inert dusts which will be discussed later

Pathologic Aspects

The most essential and ultimate reaction to accumulation of irritating dusts in the tissues of the lungs is *fibrogenesis* This is looked upon as the characteristic pathologic process in clinical dust disease Two distinct forms have been long recognized Silicosis has in time become identified with nodular fibrosis while asbestosis has been associated with diffuse pulmonary fibrosis In the light of recent experience it is now recognized that nodular fibrosis is not the one specific reaction to free silica Silica can also produce such forms as reticular, diffuse and confluent fibrosis Indeed most recent experience in berylliosis indicates that fibrogenesis is neither the only nor the most striking reaction to irritating dust Subacute pneumonitis and chronic granulomatosis as seen in berylliosis appear to be the characteristic tissue reactions to dusts of the most irritating kind

The range of pathologic reactions to irritating dusts now includes the following

1 Reticular fibrosis,
2 Nodular fibrosis tending towards conglomeration
3 Diffuse fibrosis tending towards confluence
4 Granulomatosis
5 Pneumonitis

The order in which they are listed is that of their presumed intensity of morphologic reaction It will be shown below that they are also characteristic of certain dust diseases i e of exposure to certain types of dusts or dust combinations These represent basic patterns of morphologic reactions with their special features which comprise characteristic clinicopathologic entities, the dust diseases as we know them Under standing of the latter requires familiarity with their morphologic patterns

*Reticular fibrosis** has been observed chiefly in anthracosilicosis of coal miners but is also present in silicatoses such as are produced by talc mica and other silicate dusts The most detailed description of the lesions comes from English pathologists as observed in the coal miners of South Wales The following is based on that description

Dust reticulation appears to be a foreign body reaction of the simplest type The tissue response is proportional to the amount of foreign particles Dust deposits are scattered in a lace like pattern of fine streaky

*This term is now frequently objected to perhaps rightly so It is used here on a temporary basis



processes throughout both lungs in a manner corresponding to the diffuse lattice work shadows seen by x ray The change is diffuse and symmetrical The distribution is that of lymphatic pathways and lymph depots The root glands are packed with dust while in the lung itself there is heavy storage along the interstitial tracts, in the perivascular and peribronchial sheaths as well as in the

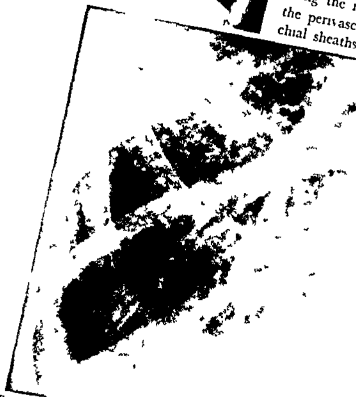


Fig 1 A and B *Reticulation Anthracosis* Exposure-coal mining

interlobular septa and subpleural tissues The appearance is best likened to patchy dust collections linked together in a vast cobweb

Dust laden phagocytes have been brought to rest along this net and transformed into fixed tissue phagocytes which then become knit together into a meshwork by elaboration of reticulum fibers These fibers are reticular, argentophile, of very fine caliber and of loose mesh, quite different in structure from other forms of dust fibrosis

There is evidence that dust reticulation is not produced by inert dusts such as coal It is most likely due to the mild irritating effect of admixtures of silica or silicates inhaled in forms in which presumably only minimal amounts of the latter are retained in the lungs The most frequent secondary change to be noted is *emphysema* which may be out of proportion to the degree of fibrosis present

Nodular fibrosis is the specific lesion produced by dust of free silica—crystalline or cryptocrystalline—inhaled over a longer period The silicotic nodule is in the nature of the "dust granuloma" which develops by a process of fibrogenesis peculiar to itself To begin with, the process is essentially an intensive foreign body reaction As free silica is a slowly acting tissue poison the cells ingesting dust particles are either killed or injured and aggregate in tubercle like nodules The peculiar fibrogenesis which follows, produces the characteristic silicotic nodules In contrast to reticulation, this fibrosis is collagenous and the fibers are coarse, close grained, non argentophile and subject to hyalin swelling This fibrosis is redundant, out of proportion to the quantity, but proportionate with the irritating potency of the dust particles This fibrosis is not linear or diffuse but has an encapsulating tendency Extending from the center, this fibrosis progresses in concentric accumulation of layer upon layer, as the nodules grow into the whorled structure composed of concentric laminae of thick hyalin fibers Once a sufficient quantity of particles has been concentrated in an area, nodulation continues to progress until the lesions have reached a 2 to 4 mm size After that they remain stationary No new lesions develop except when complicating infection continues to involve new areas

As silica tends to accumulate first in tracheobronchial lymph nodes and in subpleural lymphatics, these may be the only places showing definite evidence of early silicosis or of very mild exposures Upon adequate exposures, simple silicosis becomes generalized throughout all parts of the lungs fairly uniformly Irregularities in distribution are sometimes caused by presence of old scars which trap more dust particles in their vicinity As nodules grow in size, there is a tendency for contiguous nodules to form common capsules producing small conglomerate nodules



Fig 2 A and B *Discrete nodulation-Silicosis* Exposure—rock drilling

even in simple silicosis Central areas of necrosis develop at times in nodules by granular disintegration of aged fibers At other times calcification occurs within nodules, adding to their gritty consistency

Anthracotic pigmentation of silicotic lungs is often increased especially in cases of long exposure and may then give the appearance of anthracosilicosis (even without occupational exposure to coal dust) The shotty nodules are felt throughout the lungs which appear dark except for the areas of emphysema

Advanced nodular silicosis is characterized chiefly by progressive conglomeration of lesions in characteristic areas depending on the nature of the processes producing it

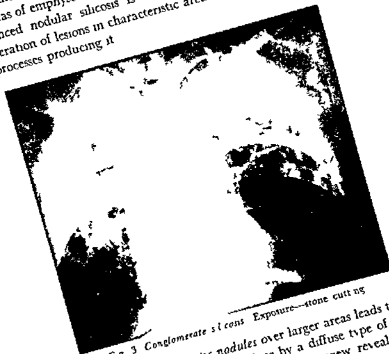


Fig 3 *Conglomerate silicosis* Exposure—stone cutting

Conglomeration of silicotic nodules over larger areas leads to massive conglomerate fibrosis Fusion takes place by a diffuse type of fibrosis of the matrix between the nodules Morphologic view reveals a diffuse matrix of hyalin fibrous tissue in which nodules may still be more or less discernible Such areas of dense fibrosis appear like rubbery hard masses, usually dark black from excessive coal pigment accumulation In the center of larger masses necrosis frequently occurs leading to cavities filled with an inky fluid without communication with bronchi

Inclined towards the belief that admixture of mineral particles other than free silica can produce it, Gardner yet remained a staunch believer in the theory that the most probable basis for massive conglomerate fibrosis is a healed infection It may now be considered a well estab-

lished fact that conglomeration of silicotic nodules can occur without any infection It is also well established that mixed dusts are frequently associated with the combination of nodular and diffuse or confluent fibrosis

Large conglomerate lesions occur most often in the upper thirds of one or both lungs Sometimes bilaterally symmetrical masses radiate from the hili into both lungs The nearer to the apices conglomeration of nodules occurs, the more likely it becomes that old healed tuberculous foci serve as starting points for the process of conglomeration Conglomeration towards the bases suggests other complicating infections, especially by pyogenic organisms The possibility of other infections is not to be denied but their practical significance is considered slight By far the most common complicating infection in nodular silicosis is demonstrably tuberculous in nature

Tuberculosis complicating silicosis can manifest itself in two distinct morphologic forms The more common manifestation is called *tuberculosilicosis* which assumes features different from either silicosis or tuberculosis It is almost indistinguishable from massive conglomerate nodular silicosis As Gardner emphasized, the point of distinction is isolated foci of caseation which may be so few and far between as to be revealed only by assiduous search More often at the time of necropsy tuberculous cavitations are found in most of the conglomerate areas The morphologic features indicate that tuberculosis modifies nodular silicosis by augmented fibrogenesis tending towards more abundant encapsulation of foci but at the same time this results in enlargement of foci and their conglomeration over large areas Tuberculous scar formation in and about the lesions enhances those aspects of nodular silicosis which resemble those of the chronic fibroid type of tuberculosis Bacteriologic studies reveal the tuberculous nature of these highly fibrotic lesions in a surprisingly high percentage of cases

It is a matter of history that the great similarity between the specific nodules of tuberculosis and silicosis has led even some outstanding pathologists to insist that silicotic nodules are just fibroid tubercles developed under the influence of dust particles of free silica The question has been repeatedly raised on the basis of clinical and x ray observations whether complicating tuberculosis truly is the factor which leads to production of the nodular lesions of tuberculosilicosis in cases where the silica particles in themselves would not have produced any or only insignificant nodulation There is evidence to indicate that complicating

tuberculosis accelerates the growth of silicotic nodules and enhances their conglomeration into lesions of even larger size

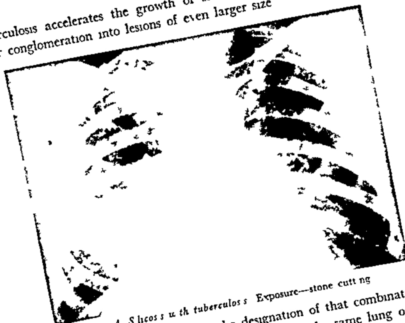


Fig 4 *Silicosis with tuberculosis* Exposure—stone cutting

Tuberculosis with silicosis is the designation of that combination in which the two conditions exist side by side in the same lung or even in the same area without materially affecting each other in their basic morphologic features Tuberculosis manifests itself here in typical manner by the presence of caseous cavities and bronchogenically disseminated fresh exudative or proliferative lesions scattered between and about the silicotic lesions Often the tuberculous process is seen to have advanced from one or both upper lung areas by breakdown of infiltrations or conglomerated tuberculous foci Often the first caseous cavitary lesion is found in the largest lesion of conglomerate silicosis in the mid or even lower lung areas Here the morphologic features reveal that a caseous pneumonic process has led to breakdown involving also large sections of the silicotic mass

Diffuse fibrosis As the term implies we are dealing here with a fibrotic process which involves the lung structures diffusely In this respect it somewhat resembles reticular fibrosis but unlike this the fibers of diffuse fibrosis are collagenous and tend to become hyalinized In this respect it is related to silicotic fibrosis from which it differs by its non nodular character The dust conditions now particularly associated with diffuse fibrosis

are the recently discovered diatomite fibrosis and Shaver's disease Also to be included here are the silicatoses, namely, asbestosis and talcum fibrosis There is also evidence that considerable diffuse fibrosis may be present together with nodulation in silicoses namely, the rapid and mixed forms

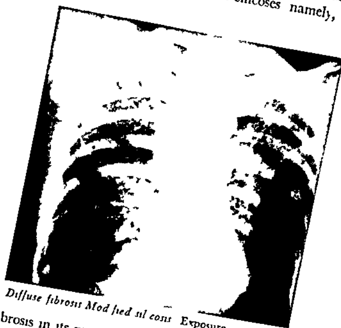


Fig 5 *Diffuse fibrosis Modified silicosis* Exposure—scouring powder

Diffuse fibrosis in its most conspicuous form, as it occurs in exposure to dust of *diatomaceous earth* has been definitely traced to cryptocrystalline free silica of submicronic particle size By inference at least it appears likely that diffuse fibrosis present in some of the other dust conditions might also be due to submicronic free silica particles Shaver's disease (bauxite) produced by exposure to fumes in the processing of alumina abrasives is characteristically a diffuse form of fibrosis, the etiology of which is still undetermined Submicronic silica particles are suspected but there is also some evidence to suggest that gamma alumina may be responsible Diffuse fibrosis has also been reported in *berylliosis* In the case of the latter it is still questionable whether the designation "dust fibrosis" is strictly speaking correct The morphologic picture of diffuse fibrosis in all these conditions is quite similar although in detail features wide differences exist between them

The characteristic gross features are voluminous yet excessively firm lungs due to ill defined areas of induration interspersed with emphy

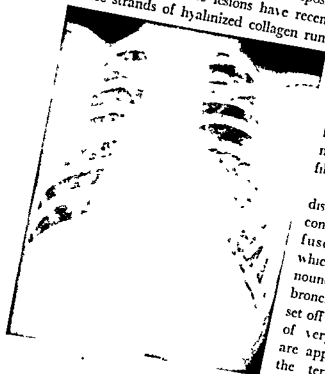
semateous areas The essential microscopic features are (a) cellular proliferation within the airspaces, (b) hyalin fibrous thickening of the alveolar walls and (c) marked emphysema in intervening alveoli



Fig 6 A and B *Diffuse fibrosis-Diatomite silicosis* Exposure—diatomaceous earth

Diatomite fibrosis is characterized by its cellular nature collagen deposition and hyalinization are less marked here The thickening of

the alveolar walls produces here a more delicate meshed fibrosis than i bauxite fibrosis In the latter the diffuse fibrosis is of a coarse meshed type due to predominance of collagen deposition and marked hyalinization In *berylliosis* too the lesions have recently been described as showing coarse strands of hyalinized collagen running between or replacing the alveoli in dense patches Emphysematous distention of intervening alveoli is a conspicuous feature in diffuse fibrosis; the more marked, the coarser the fibrosis



Asbestosis is apparently a distinctive form of pneumoconiosis It presents a diffuse interstitial fibrosis which tends to be more pronounced in the region of the bronchioles The fibrosis is set off by the asbestos fibers of very large size which are apparently retained in the terminal bronchioles



Fig 7 A and B *Diffuse fibrosis-Shaver's disease* Exposure—Bauxite processing

Gross view shows predominant involvement of the lower halves of both lungs, fibrous thickening of the peribronchial and interlobular connective tissue, adhesive pleurisy with gray fibrous tissue extending deep into the parenchyma, emphysema with bleb formation beneath the

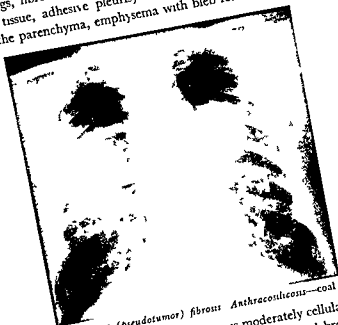


Fig 8 *Confluent (pseudotumor) fibrosis Anthracosilicosis*—coal miner

pleura Microscopically the fibrous tissue is moderately cellular, less dense or hyalin than in silicosis Extending from the terminal bronchioles the fibrosis obliterates some of the airspaces while other adjacent alveoli are distended with emphysema Asbestosis bodies are a characteristic feature They result from deposition of albuminous material and iron upon the surface of inhaled fibers of asbestos They vary in size from 5 to 50 or more micra in length and are of dumbbell shape A somewhat similar type of diffuse fibrosis has been observed also in pneumoconiosis produced by other silicates especially talcum, even with "asbestosis bodies" found in the fibrotic tissue

There are two distinct forms of reaction which have recently been discovered in workers exposed to inhalation of *beryllium* They represent the most severe forms of reaction to an irritating substance known to us

Granulomatosis is the characteristic lesion of berylliosis as acquired by workers exposed to inhalation of fumes or dust of beryllium The morphologic features are those of focal accumulations of histiocytes of

foreign body and Langhans type with variable numbers of lymphocytes and plasma cells These tubercle like foci are seen chiefly in the interstitial tissues of the alveolar walls Fibroblastic proliferation of focal



Fig 9 A and B *Granulomatosis Berylliosis (chronic)*

arrangement is usually present In addition to these focal lesions there is often found diffuse thickening of the alveolar walls by the same cellular infiltrations In patches small irregular alveoli lined by cuboidal epithelium are seen enclosed by thickened walls, while, in the intervening areas, overdistended alveoli with thinned out walls indicate the tendency to emphysema The tubercle like granulomata in the lungs are always discrete, showing no tendency to conglomeration Necrosis is not usually seen in these tubercle like lesions In the regional lymph nodes too focal lesions of the same type are usually seen in great number A tendency towards hyalinization is seen in the patches of diffuse fibrosis

Acute pneumonitis due to intensive exposure to beryllium acid fumes or dust has been reported to develop within a few hours to a few days after exposure Subacute delayed pneumonitis follows repeated lesser exposures within a few weeks Both of these are essentially in the nature of chemical pneumonias showing the usual morphological features of intensive cellular exudation in the form of bronchopneumonic consolidations scattered over both lungs in irregular fashion They are capable of slow but complete resolution

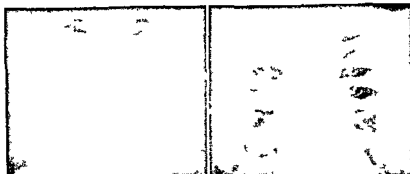
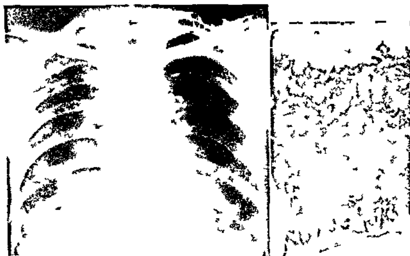


Fig 10 A and B *Pneumon t Beryll osis (acute)*

Emphysema is practically a constant morpholog c feature associated w th pneumocon ot c lesions It is all the more marked the more diffuse the fibros s present Severe bullous form of emphysema is a prominent feature especially in all the recently d scovered d ffuse fibroses (d a tomaceous earth bauxite beryllium) Severe emphysma is also com monly found in associat on with conglomerate and confluent fibrosis of silicosis tuberculos licosis anthracosilicosis asbestos s etc Emphysema



F g 11 A and B *Emphy ema and fib o n asbe to is* Attentuation of dense fibrosis by compensatory emphysema Postmortem appearance of r ght lower lobe

of much less extent is observed in discrete nodular fibrosis of simple silicosis depending of course on the density of the lesions The least

extent of emphysema might be expected in association with reticular fibrosis However, recent observations indicate that especially in anthracosis, with reticular fibrosis or even without it, with only simple dust storage in the lungs (accumulation of vast numbers of particles of coal and minerals other than silica) focal emphysema about the dust depots may be so considerable as to become functionally embarrassing



Fig 12 *Silicosis not visualized in roentgen film* Case of silicosis with tuberculosis Exposure six years tunnel drilling In right lung resected for tuberculosis silicosis demonstrated

Conclusions to be drawn from this discussion of the morphologic aspects of pneumoconiosis are as follows The basic reactions to irritating dusts — depending on degree of irritation and intensity of exposure — are dust pneumonitis and dust granuloma, ending in diffuse fibrosis and focal nodular fibrosis, respectively In final analysis then, diffuse and focal fibrosis are the basic reactions, and these are the morphologic features of greatest practical significance in clinical dust disease The underlying pathologic process of these is collagenous tissue proliferation with tendency toward hyalinization

The similarity of the hyalinosis process in chronic dust granulomas (silicosis, beryllosis), and in infective granulomas such as Boeck's sarcoid, fibroid tuberculosis, etc., is striking This similarity of lesions in such divergent conditions suggested to many workers that a common denominator elicits the same reaction in the mesenchymal tissues of the lung regardless of differing stimuli Gardner was much impressed with the theory of Fallon that a nonspecific lipid substance liberated from phagocytes (by toxic effects of silica, tubercle bacilli, etc.) produces the granulomatous reaction *

Regarding the fibrogenesis which takes place in these chronic granulomatous lesions, pathologists now hold that this occurs in the collagenous ground substance under the organizing influence of fibroblasts rather than from fibroblasts themselves The intercellular substance is a liquid material secreted by the mesenchymal cells (reticuloendothelial cells, histiocytes) Fibrogenesis is preceded by setting or jelling of this intercellular fluid under the influence of metabolic changes in the mesenchymal cells It is also well recognized that the metabolism of these cells is affected by substances absorbed by them from without or within Although the chemical nature of such substances may be very different, the changes produced in the mesenchymal tissues are identical, hence the similarity of granulomatous lesions

Clinical Aspects

The dust diseases of clinical significance are those which have been acquired in hazardous industries by exposure to injurious dust inhalation This immediately eliminates all so-called organic dust pneumoconioses Although these, too, are in a sense occupational diseases, they are not true dust diseases In byssinosis, bagassosis and tobaccosis, when real pulmonary involvement is present, it is probably due to fungus or bacterial infections On the other hand, some of the nonfibrogenic "benign pneumoconioses may acquire clinical significance

The list of clinical dust diseases now includes the following groups

1 Silicoses
2 Mixed dust pneumoconioses
3 Asbestosis and other silicatoses
4 Newer forms of dust diseases
5 Benign pneumoconioses

*A puzzling problem is furthermore the clinically recognized fact that in silicosis as well as in sarcoidosis there exists a remarkable predisposition to tuberculosis

The clinical recognition of all these forms must be based on the following three criteria

a Adequate occupational history

b Characteristic x ray features

c Characteristic clinical manifestations

These must be evaluated separately and properly correlated Correct diagnosis can be arrived at only on this basis

In evaluating the occupational history we must consider the dust factors, working conditions, and duration of exposure of the worker The dust factors have been discussed in detail but it should be remembered that these differ even for the same materials in different industries Recent experience has incriminated the exceedingly small (submicronic) particles as most harmful These are more likely to be found in industries where power drills or where highly pulverized materials are used The *industrial factors* to be considered are numerous, namely, whether the work is done in open or confined spaces, whether proper facilities for ventilation, and for dust exhaustion exist as well as for wetting of materials, and whether face masks and such protective devices are adequate Rock drilling with machine tools, sandblasting and work with highly pulverized powders in confined places, are some of the most hazardous occupations In contrast, occupations implying work in open spaces or properly ventilated shops and, with adequate protective devices even where exposure to injurious dust is involved will not as a rule result in clinically demonstrable dust disease This will only occur then in exceptionally predisposed workers Such predisposition may then be traced to some individual factor such as preexisting cardiac or pulmonary conditions

The time factors to be evaluated are the total duration of exposure its hazards and whether it was recent or old Many occupations involve exposure to inhalation of dust over many years and yet are not hazardous Not all siliceous dusts are harmful and even those which are do not produce dust disease under all circumstances On the other hand clinical dust diseases develop so insidiously that workers afflicted with them can continue to do heavy physical labor for many years in various industries Their significant dust exposure may date back 20 to 30 years At times such exposures of the past are almost forgotten by the patient and must be brought to light by detailed questioning

The occupational history must always be considered in the light of other criteria In case of a questionable history, the diagnosis must

rest on undoubted characteristic pulmonary lesions Such evidence is not too infrequently obtainable only at autopsy

Evaluation of X-ray Features Roentgen films render more or less faithful images of the gross aspects of morphologic changes in the lungs X ray features thus enable us to recognize and separate the basic morphologic reaction types discussed Reticulation, granularity, diffuse fibrosis (coarse reticulation), discrete nodulation, conglomerate nodulation, confluent fibrosis and pneumonitis can be distinguished by definite patterns in the x ray picture Insofar as these lesions are characteristic of the types of dust conditions mentioned, these dust diseases can be recognized by x ray features interpreted in light of the occupational exposure Correlation of the roentgen features with known morphologic characteristics of the lesions and with the history of exposure is of real practical importance in clinical recognition of the pulmonary dust diseases The value of the x ray is enhanced rather than reduced by full appreciation of its limitations which are the same as in other pulmonary diseases These limitations are threefold *Technical limitations* To be distinguishable from the normal structures of the lungs lesions must be of a certain minimum size, density in unit area and radio opacity (maturity of fibrous tissue) The physical phenomena of shadow summation (projection upon one another) and shadow attenuation (emphysema) determine the x ray features of pulmonary lesions Histological examination at times reveals greater extent of lesions than expected by x ray evidence and occasionally it reveals presence of pneumonoconiosis not visualized by the roentgen film * *Differentation from other pulmonary diseases* must be made by analysis of the clinical picture as a whole The x ray features of dust fibrosis are closely simulated by a large number of pulmonary diseases *Separation of the primary lesions* from its complications or its many combinations is also quite difficult or impossible from a study of x ray features alone Only careful analysis and correlation of all the evidence, can lead to diagnosis

*Recently in two cases we have obtained histological evidence of nodular silicosis from surgical specimens In one case pneumonectomy was performed for a bronchogenic carcinoma In the other case one lung was removed for excavated tuberculosis The occupational history was adequate in both of these cases, yet clinically the diagnosis could only be suspected but not confirmed because of lack of characteristic x ray features

TABLE I

ROENTGENOGRAPHIC CLASSIFICATION OF PNEUMOCONIOSES

Roentgen feature	*Morphology*	*Industrial diseases*
Reticulation with beading (pseudo-nodulation)	*Reticular fibrosis* with dust foci	Benign pneumoconiosis (anthracosis and *siderosis of soft coal workers and* welders) Silicatoses (talcum mica)
Granularity (Fine miliary stippling)	*Granulomatosis*	Beryllosis—chronic form
Bandlike and patchy (irregular densities)	*Diffuse fibrosis*	Beryllosis diatomite, bauxite fibrosis asbestosis
Discrete nodulation	*Whorled nodular* fibrosis	Simple silicosis of rock drillers stone *cutters, etc.*
Confluent patches on background of discrete nodulation	*Conglomerate* nodular fibrosis	Advanced silicosis Tuberculosilicosis Infected silicosis
Massive opacities with contraction and emphysema (pseudo-tumors)	*Massive conglomerate or diffuse fibrosis*	Mixed silicoses with infection (anthraco-silico-tuberculosis) (sidero-silico-tuberculosis)
Ground glass opacity to diffuse haze	*Pneumonitis*	Beryllosis—*acute and subacute* form. Rapid silicosis

In evaluation of the clinical picture we must distinguish those features produced by the dust reaction itself, those of the common complications and finally any unrelated superimposed disease

The clinical picture of dust disease itself is that produced by pulmonary insufficiency associated with progressive pulmonary fibrosis and emphysema This picture in its pure form is seen only in the relatively rare cases of rapidly developing dust diseases (beryllosis bauxite fibrosis rapid silicosis) Here we are often dealing with more or less subacute forms of cor pulmonale In practice most cases are very chronic forms of silicosis in which we have a complex clinical picture with three factors playing individual roles in variable proportions

(1) Pulmonary fibrosis and emphysema with varying grades of pulmonary insufficiency

(2) Complicating infections, mostly tuberculous

(3) Degenerative disease of advanced age

The characteristic feature of chronic dust disease is its slow insidious progression over many years from a subclinical stage During all this time the affected workers remain in relatively good health and are capable of performing hard labor Clinical symptoms do not usually appear until the advanced stages of the disease These patients therefore usually reach the advanced ages of 50 to 60 years or more It is in this period of life that the first signs of the aging degenerative diseases of life also make their appearance

Slowly progressive pulmonary insufficiency is always present In the minority of otherwise uncomplicated cases, this eventually may predominate the clinical picture which then becomes one of chronic cor pulmonale This phase of the clinical picture will be dealt with in a separate chapter on the functional aspects of dust diseases Complicating infections are apt to shorten the protracted course of the disease Tuberculous silicotic patients are apt to be younger but even tuberculosis tends to be more chronic when combined with silicosis Finally, the degenerative diseases of old age are also of a very chronic insidiously progressive nature The symptoms and signs of the latter are usually blended with those of the dust disease and its complications, so that to separate them in the composite clinical picture is almost impossible

(1) Silicosis

The *occupational exposure* embraces a wide range of industries Under the title *Occupational Hazards etc* (Bulletin No 41) the Division of Labor Standards of the U S Department of Labor in 1942 listed over 100 industries involving hazardous exposure to free silica These groups include the following Mining, quarries monument and building stone work, foundries, metallurgical works, chemical works, industries that produce and use abrasive powders, sandblasters, paint manufacturers, mineral filler industries (rubber asphalt etc), ceramic industries (pottery, glass etc), manufacturers of structural and insulation materials, and of decorative and optical quartz (jewels, lenses)

The x-ray features of uncomplicated (simple) silicosis differ from those of silicosis with complicating infection The x ray feature of simple silicosis with mature nodules is the characteristic snowstorm picture, where both lungs are studded with innumerable sharply defined nodular shadows of 3 to 4 mm size These are uniformly distributed in both lungs except for the costophrenic sinuses which usually appear clear due to emphysema Silicotic nodulation of smaller size and more densely seeded is seen in rapid silicosis of sandblasters and abrasive powder workers This picture is one of a dense snowstorm of tiny snow flakes This x ray appearance is simulated by the granular lesions of beryllosis and by the reticulation and beading of the fine diffuse fibrosis of silicatosis and of the benign coniosis of siderosis. Less characteristic are the x ray features of very early or advanced silicosis In very early silicosis nodulation is not so clearly defined and the x ray aspects often resemble those of reticulation with beading (diffuse fibrosis)

Classification of silicotic nodulation by stages according to the size and number of nodules in serial film studies is being gradually abandoned as of little value Progression of silicotic lesions is indicated by conglomerating tendency Although conglomerate shadows of nodular fibrosis appear quite like confluent patches of diffuse fibrosis, yet differentiation by x-ray is possible, since the discernible background of nodulation, *is distinct from the reticular background of diffuse fibrosis* Also the presence of irregular bullous emphysema in confluent diffuse fibrosis is apt to be more marked than in conglomerate nodular fibrosis Conglomeration of silicotic nodules occurs more often in the upper portions of the lungs The more extensive the conglomeration, the greater the likelihood of complicating infection, past or present

The *clinical picture in uncomplicated (simple) silicosis* is characterized by a lack of subjective complaints and scant physical signs in the chest With advancing age dyspnea and tachypnea will make their appearance with the physical signs of emphysema such as prolonged expiration, sibilant rhonchi, and accentuation of the second pulmonic heart sound Signs of interference in the pulmonary circulation overtaxing the right heart (cor pulmonale) are less apt to develop in simple silicosis, even in presence of great numbers of nodulations, than in silicosis complicated by infection

Silicosis With Infection

Chronic bronchitic infections overtake the lungs harboring dust disease in most cases We subscribe to the views expressed by Amberson that chronic bronchitis is a very common infection and that it may lead to further fibrosis of a nonsilicotic nature and advance the conglomeration of silicotic lesions We believe the chronic bronchitis develops in these patients on the basis of the bronchorrhea associated with progressive emphysema This primarily functional bronchorrhea can invite infection Eventually a persistent bronchial inflammation occurs proportionate to the degree of emphysema

In the x ray picture chronic bronchitis does not usually manifest itself although it eventually aggravates both the fibrosis and emphysema present

The *clinical course of silicosis* is made worse by the advent of chronic bronchitis To the dyspnea are now added cough, wheezing, progressive bronchospasm and viscid mucopurulent expectoration The clinical picture now becomes one of obstructive emphysema Amberson aptly

described this picture and the profound effect it had on the fate of the patients as follows ' As a result the air passages are partly obstructed, ventilation of the alveoli suffers further and subjective dyspnea increases Such a combination of forces may throw added strain on the right heart, and this, no doubt, sometimes accounts for the rather abrupt death of a patient who, previous to an attack of bronchitis, did not give any indication clinically that he was approaching the limit of his physiologic reserve'

Tuberculosis is the most important complicating infection in silicosis Some workers still hold that tuberculosis is so frequent a complication that its presence should always be considered when conglomeration of nodular lesions becomes manifest In the light of recent experience previous estimates of the very high incidence of tuberculosis (60 per cent) have to be revised downward Certainly there are variations in the incidence of complicating tuberculosis among silicotics in different localities From the West as low as 5 to 10 per cent incidence is reported Much higher rates prevail in the Eastern states but even here the rate is probably below 50 per cent The rate varies according to the epidemiologic conditions prevailing in the community where the workers live and in the racial group to which they belong There is definitely a great excess of mortality from tuberculosis among silicotics, which remains to be accounted for Gardner and his school believed their experiments established the following facts (a) Through a specific chemical effect free silica favors multiplication of tubercle bacilli present in the lungs, (b) It predisposes to fresh tuberculous infection from without and prevents healing of preexisting lesions in the lungs, (c) Tuberculosis is apt to run an acute course if a new infection is acquired when silicotic lesions are in the process of formation, otherwise they enhance the fibrogenetic action of each other, and tuberculosis is apt to be more fibrotic in the presence of silicosis

The roentgen aspects differ according to whether the process is one of tuberculosilicosis or tuberculosis with silicosis Tuberculosilicosis is often indistinguishable from conglomerate silicosis In both there occurs a slowly progressive change in the roentgen features by a merging of the lesions The closer this occurs to the apices and the more it predominates on one side, the greater the likelihood of tuberculosis Dense massive shadows against a background of generalized nodulation is the typical picture Distortion of diaphragmatic shadows and signs of pleuritic fibrosis are common in silicosis with and without tuberculosis

Gardner emphasized the changes in far advanced tuberculosilicosis and conglomerate silicosis due to contraction of the fibrotic masses and of the marked emphysema usually associated with this Much of the lung tissue is pulled upward by contraction of fibrotic masses, while the lower lung areas are overdistended with emphysema In the upper parts nodulation is obscured by massive shadows while below it is lost in the overpenetrated emphysema As a consequence *the film may fail to reveal the nodulation to suggest the silicotic origin Such cases present a difficult problem in diagnosis which can be resolved only in the light of exhaustive occupational history and careful analysis of the clinical picture* *

The roentgen features of tuberculosis with silicosis are those of tuberculosis *superimposed on a background of silicotic nodulation* Typically tuberculous excavations, bronchogenic spreads, and pleural effusions *establish the diagnosis In these cases the x ray findings are more likely* to be misinterpreted as simple tuberculosis overlooking the silicosis Silicotic nodulation and disseminated nodular tubercles are difficult or impossible to differentiate Here again the diagnosis must be based on establishment of the occupational hazard

In the clinical picture separation of cases of tuberculosilicosis and tuberculosis with silicosis is not so clear except in the infrequent cases of exudative and more rapidly progressive tuberculosis Chronic pulmonary tuberculosis complicating silicosis need not change the clinical picture until it has become far advanced In cases of tuberculosilicosis we are dealing with two equally chronic processes the symptoms and signs of which are blended into a chronic, long protracted disease. *Tuberculosilicosis is often simulated by the latency of incipient tuberculous lesions* which often last for years This latent period is even more *protracted under the influence of silicotic fibrosis* Sooner or later the silicotic patient with complicating tuberculosis will begin to complain *of weakness, fatigue and loss* of weight in addition to the preexisting dyspnea Once a breakdown of lesions begins, progress becomes noticeable by malaise cough with expectoration, localized rales in the chest, and elevated sedimentation rate Finally the diagnosis may become defi

*In early *silicosis too the x ray features may not reveal the condition until complicating* tuberculosis supervenes The differential diagnosis from tuberculosis alone is then a most difficult problem often to be solved only by necropsy The difficult question of *when does predisposition to tuberculosis* begin to operate in silicosis also comes up in these cases Both these questions must be answered from case to case by careful consideration of the occupational and clinical histories

nite by occurrence of hemoptysis, acute pleurisy and frequently enough by a sputum culture showing tubercle bacilli

Other respiratory infections are more frequent and are also apt to be more severe in silicotics Somewhat increased incidence of infections of the respiratory tract is indicated by our experience with silicotics in the northeastern parts of the country As they advance in age and in the extent of the pulmonary lesions, silicotics become increasingly susceptible to recurrent attacks of the seasonal respiratory infections of viral or mixed bacterial origin These infections tend to become increasingly severe bronchopneumonic inflammatory processes Their resolution is often slow and incomplete Suppurative pneumonitis with abscess formation or with development of chronic bronchiectatic disease is also somewhat more common among silicotic patients Superimposed as these infectious lesions usually are on far advanced conglomerate silicotic lesions their x ray manifestations may remain far less conspicuous than indicated by the seriousness of their clinical features Death due directly to complicating (pyogenic) respiratory infections is not uncommon in silicotics Indirectly by way of cor pulmonale such infections often become fatal in these patients

Mixed Dust Pneumoconiosis (Modified Silicosis)

This form is produced by dusts containing free silica mixed with other dusts which may be silicates or nonsiliceous materials The occupational history reveals many industries known to involve exposure to free silica combined with unsuspected dust mixtures but also industries in which the high content of free silica dust is unsuspected It is most conspicuous in the mining industries namely coal iron etc ore mining This form is best known to us as it occurs in anthracosilicosis of miners which was studied exhaustively by British investigators on the miners of South Wales

The roentgen features here are chiefly those of reticulation with or without nodulation with progression to confluent massive (pseudotumoral) fibrosis

Reticulation appears in the x ray film as a network of lace like pattern laid out between the linear shadows of exaggerated lung markings Its mesh is delicate and hazy in the periphery and becomes more coarse and sharp towards the center of the lungs When reticulation is combined with nodulation the lung fields may suggest the appearance of rough orange peel with so many ill defined small ringlets within a

fairly coarse mesh woven about numerous larger knots the silicotic nodules The latter are smaller than the usual mature silicotic nodules. They are discrete from one another but tend to merge into the surrounding reticulation The lesions are usually most dense in the mid lung fields and *it is here where they tend towards confluence* The area first becomes hazy, then fluffy and as its opacity increases with density of the lesions, massive pseudotumoral shadows are produced These massive shadows become more and more sharp in outline, accentuated by the simultaneously increased emphysema of the surrounding lung areas

Complicating tuberculosis is less common in this form of silicosis but anthracosilicotuberculosis is by no means uncommon among coal miners and trimmers Complicating tuberculosis may be present without affecting the usual x ray features in any way Indeed complicating tuberculosis is mostly unsuspected by the x ray features and is revealed often only at postmortem examination Rarely *cavities developing in or about the massive shadows reveal the presence of frank tuberculosis*

In *the clinical picture* early appearance and progressive character of pulmonary insufficiency is a striking feature in this form Often dyspnea and tachypnea reveal the true extent of the pulmonary fibrosis unsuspected from the x ray features because of the amount of emphysema The same is true for complicating tuberculosis which may be present quite unsuspected even in spite of persistent negative sputa The patient *with anthracosilicotuberculosis with extensive pseudotumerous fibrotic* masses is more apt to die of right heart failure than of tuberculosis

Silicatoses

In this group by far the most important form is asbestosis Other silicates namely talc mica soapstone have also been reported as producing pulmonary fibrosis In the latter group *it is still open to* question whether admixtures of free *silica are not responsible for the* fibrosis In asbestosis we are dealing with a rather severe form of diffuse fibrosis which *is in* a class by *itself*

Asbestos (A hydrated magnesium silicate) in form of fibrous chrysolite has a *harmful* potency probably due to the mechanical action of the stiff fibres when lodged in the terminal airpassages Occupational exposure occurs *in a number of trades where* asbestos is used for packing insulating fireproofing etc It takes approximately seven to nine years of exposure to a *fairly high concentration of the dust to produce*

the disease which when once established is progressive even after cessation of exposure

The *roentgenographic features of asbestosis* do not become apparent until the disease is well advanced, when it begins to show a fine widespread stippling-granularity of uniform density As this increases to a point where the granules tend to become confluent the lung fields assume the ground glass appearance of a diffuse haze Upon this ground glass background considerable superimposed reticulation also becomes evident These features become marked over the base of both lungs while the upper parts may remain remarkably clear Emphysema may mask the fibrosis of asbestosis often to a point where the x-ray fails to reveal much of the severe anatomical changes present Involvement of the pleura with contracting adhesions over the pleurodiaphragmatic and pleuropericardial surfaces produces the irregularities of "porcupine heart shadow and "porcupine' diaphragms which often suggest the diagnosis of asbestosis earlier than do the other x ray features

The *clinical picture of asbestosis* is marked by a degree of dyspnea which is entirely out of proportion to the x ray appearance of the lesions With this occur some cyanosis and considerable cough and expectoration of viscid sputum in which asbestosis bodies can be detected, especially when complicating infection is present Tuberculosis is not a prominent complication but pyogenic infections are frequent and chronic bronchiectatic disease is a common complication

Talcum Fibrosis

Talc (a hydrous magnesium silicate) has repeatedly been reported to produce pneumoconiosis in workers inhaling the dust in mining and milling of talc and in industries (paint, linoleum, paper and cosmetics) where talcum is used or mixed in fine powder form The roentgen features first are of a reticulation type of fibrosis and later, progressive pseudonodular beading In advanced severe cases, plaques of radioopaque dust deposits may be seen irregularly in subpleural location especially over the lower parts of both lungs The associated emphysema is usually quite severe and results in the clinical picture of progressive pulmonary insufficiency

Newer Forms of Dust Diseases

In this group we include rapid silicosis, diatomite and bauxite fibrosis and beryllosis The common characteristics of this group are (1) They represent more recently discovered dust diseases, (2) more than all

others they damage the lungs more severely and lead to greater morbidity, disability and fatality, (3) their lesions are of the nonnodular diffuse type, and (4) their development is rapid, leading to demonstrable fibrosis in a few months to a few years

RAPID SILICOSIS

This condition was first identified in manufacturers and packers of abrasive soap powders fairly recently (1930) Since then other cases of so-called acute silicosis have been found among sandblasters in enclosed tanks and high power drillers of tunnel rock The exposure periods have been as short as 1½ years and survival has been as short as one year after first signs of dyspnea have appeared The lesions have been described as diffuse to confluent fibrosis (dust pneumonia) The x ray features vary between a fine haze to large confluent pneumonic patches The clinical picture is one of pulmonary insufficiency with dyspnea tachypnea and cyanosis progressing to cor pulmonale within a few months to a year In spite of this rapid development some of these patients have shown evidence of complicating tuberculosis

DIATOMITE FIBROSIS

This is a recently discovered dust disease, produced by the dust of diatomaceous earth consisting of amorphous deposits of siliceous skeletons of small prehistoric aquatic plants Clinical and experimental evidence indicates that both crude and fluxed calcined diatomite causes fibrosis but the latter is more potent It has been shown that when the material is calcined by ignition at 1200°C large parts of it turn into microcystalline crystobalite which is a highly potent free silica It produces a diffuse form of fibrosis in the lungs

Exposure occurs in workers of quarries and of factories making filter candles insulators and absorbent powders etc *Length of exposure* before demonstrable x ray changes and symptoms (dyspnea etc) has *varied from 12 months or less to from three to five years*

The *roentgen features* to begin with are those of fine reticulation *of sharp lace-like appearance which later becomes increasingly blurred* and then hazy and fluffy Reticulation becomes increasingly coarse with *thick stripes radiating toward the roots* Emphysema increases in extent as the lung fields show an increase of shadows becoming of a fluffy ground glass appearance Finally irregular patchy and massive confluent shadows appear in the upper and mid lung fields and spontaneous pneumothorax becomes a frequent complication

In *the clinical picture*, here too progressive pulmonary insufficiency

predominates and leads to cor pulmonale pacing the development of the pulmonary changes, which vary considerably in different individuals under different processing

Bauxite Fibrosis (Shaver s Disease)

This condition also has been discovered more recently in workers exposed to fumes escaping from furnaces in the processing of bauxite in the manufacture of aluminum abrasives These fumes contain aluminum oxide and silica Both these substances are suspect as etiologic factors in the severe diffuse fibrotic pulmonary changes of the exposed workers Studies have only begun as to whether we have here a silicosis without nodules Shaver reports marked differences in individual susceptibility For 10 patients who died of the disease the average length of exposure was slightly over six years Some workers showed x ray and clinical evidence of the disease after three years exposure

The roentgen features begin with a granular haze over the upper thirds of both lungs which advances in area and intensity Eventually the mediastinum becomes wide heavy fibrotic strands radiate into the lung fields which contract with distortion and elevation of the diaphragm Marked emphysematous changes are constant complicating pneumothorax is frequent

Here too the clinical picture is predominated by emphysema and pulmonary insufficiency indicated by early and progressive dyspnea No predisposition to tuberculosis has been noted

Berylliosis

This is the most recently discovered dust disease It is perhaps the first dust disease definitely known to be entirely unrelated to silica in any form It is also the most severe form in the sense that even though exposure is short in time and mild in intensity the lesions are often acute and extensive Available evidence points to beryllium as the causative agent although chronic granulomatosis has not yet been reproduced in animals

Most cases have occurred in plants processing beryllium from ores A considerable number have been reported among workers in fluorescent lamp manufacture in preparation of lamp phosphorus in manufacture of beryllium alloys of sign tubes of beryllium crystals for radios, in salvage of fluorescent lamps, etc Sporadic cases have occurred in the neighborhood of plants probably as a result of exposure to beryllium contained in exhausts

Data on exposure are still inadequate Machle quotes evidence indi

cating that 100 micrograms of beryllium in a cubic meter of air proved to be a harmful concentration for inhalation His studies also suggest that the more soluble beryllium compounds (fluorides, sulfates) tend to produce acute forms, while the less soluble ones are responsible for chronic beryllioisis

Machle holds that differentiation between acute and chronic forms is arbitrary, and that transitions from the former to the latter exist Acute beryllium pneumonitis and chronic beryllium granulomatosis represent distinct pathologic, roentgenographic and clinical pictures

Beryllium pneumonitis develops within a few days with symptoms of dry cough, increasing dyspnea and cyanosis, substernal pain, and prostration, with little or no fever The disease runs its course in from a few weeks to about five months Death may occur in the first three weeks, but after that resolution is the rule The morphologic picture of dense cellular exudation without polymorphonuclear leucocytosis has been described before The roentgenogram shows soft opacities covering both lung fields with greatest density in the midfields Clearing of roentgen opacities is slow but practically complete with resolution of the clinical picture

Chronic beryllium granulomatosis is characterized by delayed onset long chronicity and poor prognosis The disease is often delayed by months and years following exposure and its onset is very insidious First symptoms are fatiguability, weakness, and loss of weight Eventually localizing symptoms of cough dyspnea, pain in chest, cyanosis and clubbing of fingers appear These increase progressively towards a chronic cor pulmonale Finally orthopnea and symptoms of cardiopulmonary decompensation with congestive failure are terminal Fatality rate has ranged from 15 to 30 per cent

The *roentgen feature* characteristic of chronic granulomatosis is a granularity, i e , a fine sandlike pattern of stippling distributed densely throughout both lungs from apex to base As fibrosis proceeds in the granulomatous lesions, the x ray pattern becomes both reticular and nodular, with the fine granularity in the background Eventually prominent x ray features are a coarse striped fibrosis, nodular coalescence leading to irregular opacities, contraction in some lung areas and emphysematous overdistention in others, distortion of diaphragm, and spontaneous pneumothorax

THE "BENIGN" PNEUMOCONIOSES

In this group we have included conditions due to inorganic dusts other than silica, which are not capable of producing a significant amount of pulmonary fibrosis Gardner who termed this group "benign" (nonspecific), implied that these conditions represent only a dust storage with pigmentation, that they produce no symptoms, disability or predisposition to infection, particularly not to tuberculosis ('They only cast shadows on the roentgenogram") He included anthracosis from coal and graphite, and siderosis from iron Baritosis from baryta and stannosis from tin have recently been added by Pendergrass to this group Aluminosis from artifical abrasives and other inert dust conditions also belong here (carborundum, emery, etc)

The important conditions are *anthracosis* as seen in workers inhaling much coal dust especially in handling of soft coal, and *siderosis* as seen in electric arc welders, metal grinders in foundries etc Recent evidence points to the fact that although here the reactive fibrosis remains insignificant and is never hyalinized, yet it is frequently sufficient to lead to a fine reticulation In anthracosis, it is now established that the development of so much focal emphysema may result as to cause as much or even more progressive disability than that caused by simple nodular silicosis

The *roentgen features* appear as a fine reticulation with beading in a background of exaggerated normal lung markings or as pseudo nodulation The latter is particularly conspicuous in siderosis in which the radioopaque metallic deposits in the tissues often simulate nodular fibrosis

The clinical picture in this group is usually not characteristic except in cases of anthracosis associated with emphysema The latter invites complicating bronchitic infections and eventually leads to progressive pulmonary insufficiency

Differential Diagnosis

For the most part the differential diagnosis of dust diseases is not problematic as long as we adhere to the principle that such disease should be considered only when the occupational history of exposure is adequate and is corroborated by x ray and clinical features compatible with such a diagnosis Differential diagnostic problems occasionally arise when workers exposed to dust in their occupations develop a chronic pulmonary condition, the x ray and clinical features of which

simulate — at least temporarily — those of pneumoconiosis, raising the question of etiology of the pulmonary lesions

The pulmonary conditions which may simulate pneumoconioses especially by their x ray features include the following groups

(1) *Chronic infections* Tuberculosis (chronic hematogenous) *Mycoses* (aspergillosis blastomycosis actinomycosis coccidioidomycosis, histoplasmosis etc.
(2) *Malignancies*
(3) *Carcinomatosis* lymphoblastomatosis (disseminated forms)
(4) *Allergies* bronchiolitis Loeffler's syndrome disseminated lupus erythematosus periarteritis nodosa.
(5) *Vascular lesions*
(6) *Miscellaneous*
- Hemosiderosis.
- Passive congestion (mitral stenosis)
- Idiopathic pulmonary fibroses
- Bronchiolectatic disease
- Scleroderma.
- Irradiation fibrosis.
- Adenomatosis

The most frequent and most difficult differential diagnostic problem is that between dust disease and tuberculosis, i.e., the question of whether we are dealing with tuberculosis alone or combined with dust disease It is not at all uncommon to see patients with frank signs of tuberculosis who have an adequate history of potentially harmful dust exposure but the corroborating x ray features of pneumoconiosis are lacking more or less completely This is not surprising if we remember that not all exposed workers develop dust disease The question of when predisposition to tuberculosis begins to operate under exposure to inhalation of free silica particles, remains to be determined. In the absence of definite nodular fibrosis, the diagnosis of silicosis remains questionable

Functional Aspects

The functional implications of dust diseases are under investigation by methods which have only recently been introduced and are still in process of elaboration. Much progress has already been made but much yet remains to be learned It is now recognized that the principal factors responsible for disturbances in the function of lungs affected by dust disease, are fibrosis and emphysema. These two conditions, so commonly found together in most forms of dust diseases are associated in a manner which yet remains to be clarified It is clear, however that the association is of functional significance since both fibrosis as well as emphysema may bring about changes in the lungs which affect the function of the organ in all its aspects.

The data obtained by all the function tests when correlated by the graphic method of analysis recently elaborated afford enough information to determine the nature of impairment in all aspects or in any phase of pulmonary or cardiocirculatory function

These functional studies, however, are too elaborate and too time consuming to permit testing large numbers of workers, and the correlation between the finding in these functional tests and the clinical signs and symptoms in the cases of pneumoconiosis so far studied has not been too good The search continues for a more simple test and one which would give better agreement with the clinical findings Most recently Pelnar claims to have found such a test in his "Respiratory Quotient Loops" This rests on the principle of continuous analysis of the expired air and registration of the respiratory quotients The curves so obtained ("Loops") afford information on the patient's functional capacity by their position, direction, shape and size This procedure which makes use of recently developed techniques for continuous analysis of expired air has the advantage of simplicity and affords important information regarding the ventilatory process and its response to exercise However, an adequate evaluation of distribution diffusion and circulation requires additional procedures

Pulmonary fibrosis tends to lead to hardening and retraction of the tissues of the lungs with the result that the capacity to hold the normal volume of air is eventually decreased in all cases with fibrosis of considerable extent It is yet so that the rest volume of the lungs is often increased and breathing, especially in exercise, tends to start from this elevated functional level The effect of fibrosis upon the movement of air and flow of blood from and into the lungs (ventilation and circulation) differs according to the site of the fibrotic changes In silicosis of conglomerate type the fibrosis involves especially the peribronchial and perivascular interstitium with resulting increase in resistance to the movement of air and flow of blood into and from the lungs in proportion to the extent of the rigidity of these structures In diffuse fibroses especially the newer forms (berylliosis, diatomite silicosis, Shaver's disease) the fibrosis involves the alveolar structures, the thickening of which leads to interference with gas diffusion

Emphysema leads to overdistention of the lungs and results in fixation of the organ in the hyperinflated state

It lies in the nature of the lung changes that the separate functions

are affected by fibrosis and emphysema in a different manner and to a different extent

(1) *Volumes* *Total capacity* tends to be decreased by fibrosis while it is normal or increased by emphysema *Residual volume* While emphysema is characterized by progressive and marked increase in residual volume, in fibrosis the increase, if any, is slight or moderate However, in fibrosis with slightly increased or normal residual volume in presence of marked reduction of total capacity, the ratio of total capacity to residual volume may be increased as much as in emphysema with a high total capacity compensating for increased residual volume

(2) *Ventilation* *Vital capacity tends to be reduced in both fibrosis* and emphysema In fibrosis the trend is towards reduction of the complemental air while in emphysema the reserve is encroached upon by the rising residual volume In fibrosis there is marked trend towards hyperventilation by increased rate and tidal volumes In emphysema such compensatory hyperventilation becomes less and less feasible as the process progresses *Maximal breathing capacity* suffers more reduction from emphysema than from fibrosis in which compensatory hyperventilation remains feasible to a considerable extent

(3) *Circulation* Increased pressure levels in the pulmonary circulation are apt to develop earlier and more often in fibrosis In emphysema circulation is obstructed only in the most severe cases and advanced stages

(4) *Distribution* In emphysema poor mixing of the air is a frequent disturbance which is apt to result in hypoventilation of perfused areas, while in fibrosis ventilation of *nonperfused areas* may result in increased deadspace

(5) *Diffusion* is rarely affected by either fibrosis or emphysema Only in the few cases of new forms of fibrosis (beryllosis, Shaver's disease and perhaps in the rare case of very severe diffuse fibroses) does diffusion of gases become affected by thickening of the breathing surface membrane

Concluding from the above the chief functional disturbance is *ventilatory insufficiency* as manifested by *restricted maximal breathing capacity* Also, there may be *defective air distribution* when emphysema predominates or *defective blood distribution* when fibrosis predominates Both lead to gas exchange disturbances, namely to CO_2 retention in the former and O_2 unsaturation in the latter Disturbances in gas exchange develop only in more extensive forms of fibrosis or emphysema and even

in these it will be apparent mostly only in exertion *Respiratory insufficiency* at rest is not observed until the late phases The same is true for listurbances in circulation which develop only in extensive forms of brosis or emphysema and then only in the advanced phases

As indicated above in dust diseases fibrosis and emphysema progress parallel but beyond a certain point they become mutually exclusive In massive fibrosis the lungs tend to contract and emphysema becomes restricted to localized bullae or blebs In acute more rapidly progressive or diffuse forms of fibroses (new form of dust diseases) it is fibrosis not emphysema which plays the predominant role in leading to pulmonary insufficiency It is noteworthy that development of cor pulmonale of subacute or chronic type is the rule in these forms

Clinically and functionally significant emphysema is found mostly in the more chronic forms (silicoses) in which fibrosis is slow in its development but particularly in those forms in which the fibrosis is extensive in its spread but not massive in degree Anthracosilicosis is perhaps most representative of this form Indeed recent experience indicates the development of marked emphysema even in absence of fibrosis (due to dust reticulation alone) in anthracosis Pulmonary insufficiency due to predominant pulmonary emphysema takes a more protracted course Here too we observe development of cor pulmonale of the chronic type which is however often masked by other complications — mostly infections — or degenerative diseases — which cut short the patient s life often before pulmonary heart failure develops

Compensatory lung function develops in pneumoconiosis — no doubt — as it does in other chronic progressive diseases The nature of this compensation is still an open question It is safe to assume that compensation rests within those lung areas remaining intact between those involved by fibrosis Observations indicate that these overexpand and eventually they become permanently emphysematous

The usual assumption is that emphysema develops only as a result of fibrosis but there is ample proof that it can also develop without fibrosis when lung areas are involved in simple dust storage This has been described as "*vicarious focal emphysema* of mechanical origin As involved areas are unable to expand adjacent alveoli must enlarge to take up the stretch

In case of fibrosis emphysema also is commonly assumed to be of the same nature Contraction of fibrous tissue causes the airspaces in the rest of the lungs to overdistend in order to fill the chest This is the

usual explanation This is described as "*compensatory emphysema*" and this rather than fibrosis is believed to be responsible for dyspnea

As indicated above clinical experience does not show proportional relationship between fibrosis and emphysema In some cases emphysema is far out of proportion to the extent of fibrosis and vice versa

We have recently promulgated the concept of functional emphysema of truly compensatory nature—associated with an increase in the breathing surface of the compensating alveoli—which we believe is present in early phases or moderate forms of fibrosis In severe forms of fibrosis nature's effort at compensatory expansion results not in functional but structural emphysema (bullae, spontaneous pneumothorax) and pulmonary insufficiency We believe that compensatory emphysema far from being the cause of dyspnea, delays its advent in pulmonary fibrosis

Clinical experience does not confirm the existence of direct relationship between the degree of dyspnea and the extent of pulmonary fibrosis or emphysema or both In spite of much emphysema—focal or diffuse—patients are often free of dyspnea and able to work In contrast, dyspnea is often severe with but little fibrosis or moderate emphysema Such dyspnea tends to become apparent first only on exercise, when it is clearly elicited by the increased circulatory demand of exercise The normally phenomenal capacity of the lungs to transmit an increased amount of blood by increasing its capillary bed is lost here We believe the reason is that the available reserve has been taken up by compensatory emphysema The latter is associated by a proportionate increase in the bed of the pulmonary circulation This is reflected also in the hypertrophy of the right heart developing under such circumstances as a part of chronic cor pulmonale which — we believe — is at first compensatory in nature Congestion of blood in the capillaries occurs here not in the fibrotic but in the emphysematous lung areas When pulmonary heart failure develops, it is apt to be associated with increased cardiac output

Nature of Dyspnea in Pneumoconiosis

Clinical experience has shown wide discrepancies between the extent of lesions by x ray evidence and symptoms of pulmonary dysfunction chiefly dyspnea Equally evident is the lack of relationship between clinical dyspnea and the objective evidence of disturbed function by the tests employed so far It is not always possible to account for the dyspnea which is present in some cases by the demonstrable extent of

fibrosis or emphysema or their combinations In other cases it is difficult to account for the lack of dyspnea in presence of extensive degrees of fibrosis or emphysema In the light of accumulated evidence it has become increasingly clear that dyspnea is a respiro circulatory distress signal of great complexity It may have its origin in a multiplicity of reflex stimuli which can respond separately as well as in coordination Ample evidence has accumulated to substantiate the concept that proprioceptive impulses from all the structures implicated in volume regulation ventilation and circulation originate the state of dyspnea As applied to pneumoconiosis dyspnea is at times the signal for disturbed volume regulation or of difficulty in the breathing mechanisms at other times it is the signal of congestion in the pulmonary circulation, rarely, perhaps, it indicates approaching actual air hunger in the sense of CO_2 excess or O_2 want Probably most often, the sensation is elicited by the combinations of these stimuli enhancing each other so as to rise above the dyspnea threshold

Disability Estimation from Medicolegal Standpoint

Clinical experience has shown that functional studies are no substitutes for clinical estimation of disability which varies from case to case regardless of identical occupational factors and similar extent of disease Functional tests have been of great help in guiding clinical judgment They have revealed functional impairment unsuspected from clinical criteria in some cases More often they failed to reveal functional impairment in cases of disability suspected from the clinical findings

In medicolegal disability estimation experience has shown that the basic problem is discrimination between disability due to natural causes and that acquired by the occupational disease Since the majority of disabled workers are in that age period when these two forms of disability are present in combinations we must realize that disentanglement of these causes is a hopeless task

We are now convinced that disability evaluation is a matter of seasoned clinical judgement acquired by experience

We must learn to evaluate separately and then correlate two factor complexes 1 *The disease and its complications,* 2 *The individual*

The disabled silicotic is mostly a middle aged man who has lived and worked with his disease for many years We must decide whether his disease or complications recently progressed to disability, and what other

factors arose to bring about his disability at this time, whether temporary or permanent Other such factors as alcoholism and old luetic infection are found Mostly the aging processes as progressive arteriosclerotic cardiovascular disease, obesity and skeletal and postural changes quite independent of his dust disease precipitate disability

The psychosomatic aspects of disability must also be reckoned with in our evaluation One often finds workers with obviously disabling dust disease insisting on ability to work, while others with no real physical disability are emotionally disabled How emotional difficulties can aggravate breathing disturbances and produce dyspnea can be scientifically explained

Treatment

It should be obvious that there can be no effective treatment for established lesions of pneumoconiosis It is conceivable however that upon interruption of exposure and cessation of dust accumulation self cleansing efficiency of the lung may be so improved as to gradually rid itself of much dust not yet fixed by fibrosis in the pulmonary tissues *In that sense immediate change to work not involving dust hazard may* be said to be not only prevention but to some extent also treatment of dust disease

The real treatment lies in the prevention of complications and their treatment when existing As shown before, infections and-or progressive pulmonary insufficiency overtake sooner or later most cases of pneumoconiosis

TREATMENT OF TUBERCULOSIS

In industrial medical practice our largest task is the prevention and treatment of tuberculosis in silicotics Since we know that every silicotic is a potential tuberculous patient continued observation is in order to anticipate development of this complication

From the standpoint of treatment of complicating tuberculosis the *previously discussed distinction between tuberculosilicosis* and silicosis with tuberculosis is helpful In tuberculosilicosis the lesions are so fibrotic that routine rest treatment could hardly be expected to affect their progress *while more radical treatment is hardly* ever required and still less feasible These patients tend to become incapacitated more rapidly by the progress in their functional limitations aggravated by the added tuberculous fibrosis

In silicosis with tuberculosis fresh bronchogenic spreads exudative infiltrations and progressive cavitations often call for treatment of a

frank tuberculous process no different from that in ordinary progressive tuberculosis However the treatment must be more conservative than if the lungs were free of silicosis Exceptionally even collapse therapy is feasible in some cases with lesser degrees of silicosis Its possibilities should certainly be explored when the indications are urgent

Antibiotic therapy of tuberculosis combined with silicosis has not yet had an adequate trial Not enough is known as yet of the effectiveness of streptomycin or "P A S", hydrazide derivatives of isonicotinic acid or their combinations A few instances of early favorable results have already been observed There is every reason to believe that in silicosis with tuberculosis, exudative infiltrations of the latter will respond just as they do in cases without silicosis In the more chronic productive, fibroid type of tuberculosis little effect has been observed from chemotherapy, and it will probably be so in the even more fibroid lesions of tuberculosilicosis However, future experience will better determine the indications for and the results to be obtained from antibiotic therapy of silicosis complicated by tuberculosis *

Complicating purulent infections often require treatment with antibiotics by injection and by aerosol inhalation Surgical drainage of pyogenic abscesses is at times called for in complicating infections

Treatment of pulmonary insufficiency aims at slowing of its progress from emphysema to cor pulmonale by way of bronchorrhea, cough, expectoration and increasing dyspnea The modern therapeutic measures employed in the management of emphysema, namely, inhalation of bronchodilator aerosols, are useful for the relief of these symptoms The need for restricting exercise may now be determind by modern functional tests estimating working capacities

The treatment of progressive cor pulmonale is entirely symptomatic as illustrated in Table II

*Experience obtained since the above was written seems to confirm these pred ctions in regard to antibiotic therapy of combinations of s licosis and tuberculosis In silicosis with tuberculosis ' the latter responds to antibiotics as tuberculosis alone does [illegible]

prolonged Pneumoperitoneum is now used increasingly in some of these patients chiefly because of its favorable effect also on the associated emphysema The effect of chemotherapy in cases of s licotuberculosis still remains as uncertain as often the diagnosis is almost to the very end In these cases however a trial with antibiotic therapy is justified whenever the suspicion of compl cating tuberculos s has arisen

TABLE II

CLINICAL PHASES OF COR PULMONALE AND THEIR TREATMENT

Clinical features	*Functional status*	*Complications*	*Treatment*
I Bronchial phase—adequate compensation—long period			
Signs of primary pulmonary or cardiac condition and those of progressive emphysema	Progressive restriction of exercise capacity with dyspnea and cyanosis on mild exertion	Bronchorrhea Recurrent bronchial infection	Prevention of bronchial infection their treatment with penicillin by inhalations and injections
II Pulmonary phase—inadequate compensation—variable period			
Signs of emphysema dyspnea cyanosis on exertion marked Tachycardia central venous engorgement.	Ventilatory insufficiency Gas exchange disturbance Progressive anoxia Increased cardio-circulatory embarrassment	Persistent bronchial infection aggravated by periodic attacks of pulmonary congestion.	Vaponephrin inhalations. Aminophyllin. Penicillin. Abdominal belt. Pneumoperitoneum.
III Cardiac phase—decompensation—short period			
Predominant right ventricular failure dyspnea and cyanosis marked orthopnea slight.		Few bouts of congestive failure alternating with short periods of decompensation	Digitalis Mercurials Periodic oxygen inhalations.
Total heart failure orthopnea marked dyspnea and cyanosis		Recurring attacks of pulmonary edema	Positive pressure oxygen inhalation Phlebotomy

Aluminum treatment of silicosis is now under trial in this country and Canada The claim has been made that inhalation of finely divided metallic aluminum powder can prevent the harmful effect of silica particles currently inhaled and even of those recently accumulated in the air spaces Gardner reported that hydrated silica may be used with good results in not only inhibiting the action of silica but also ameliorating the symptoms of silicotic patients

Canadian workers demonstrated in animal experiments that finely divided aluminum powder would prevent development of silicosis in spite of exposure to amounts of silica usually adequate to produce lesions They also showed that the effect of aluminum is in large part due to the formation of an insoluble coating or gelatinous aluminum hydroxide about the silica particles This coating prevents the solution of silica and thereby the production of lesions This mechanism of action of aluminum powder is considered as supporting the solubility theory of the action of silica However in a recent publication Heffernan contends that the results with aluminum powder confirms his concept that silica is at its maximum chemical activity in the aerosol state—provided the particles are small enough, rather than with the obsolete theory that silica exerts effects by slow transformation into silicic acid Active silica surface may be rendered inert b verting ae hydrosol Th better method is by satisfying ca surf g dust pa ticles with aluminum which f t a surf aluminum The chemical reaction of the of sil with alum

num may be described as adsorption Silicates are such "adsorption compounds"

The use of aluminum powder for dusting the air in work places and for direct inhalation by workers exposed to silica hazards was undertaken on the basis of the animal experiments, the results of which were confirmed at Saranac by Gardner and his associates

The results of the clinical tests carried out so far are inconclusive In a recent report on the best controlled clinical experiment it is concluded 'An impressive degree of subjective improvement was reported by the majority of the individuals in both groups (treated and untreated) In the aluminum treated group, no objective changes were observed which could be convincingly attributed to the metallic therapy"

The true prevention of dust disease consists, of course, in the radical elimination of all dust hazards in industries The methods employed in the prevention of hazardous dust concentration in the air inhaled by the worker include the following (1) wetting processes to precipitate the dust at its point of origin, (2) exhaust ventilation to constantly reduce the concentration of dust at its point of origin, (3) use of masks and respirators by workers exposed to inhalation of dust where its concentration is not reducible to safe levels The most efficient application of these methods in the respective industries in question represent problems which differ from one industry to another and in some respects differ even from one plant to another in the same industry These are important industrial engineering problems which have been worked out by specialists in the various fields of industrial hygiene and are beyond the scope of this presentation

Last but not least, prevention of dust disease includes preemployment and periodic medical examination of exposed workers The former will eliminate those with pulmonary disease or with predisposition toward dust accumulation in the lungs The latter will eliminate those showing individual predisposition by detecting signs of earlier dust accumulation in the lungs

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lung changes from

BAGASSE DISEASE

By ANDREW L BANYAI, M D and J WINTHROP PEABODY, M D

Jamison and Hopkins (1941) are credited as being the first to describe a pulmonary disease due to the inhalation of the dust of dry sugar cane from which the sugar has been previously extracted Bagasse is the name for this waste of sugar cane According to Browne, the chemical composition of bagasse is cellulose, 55 per cent, xylan, 20 per cent, araban, 4 per cent, lignin 15 per cent, acetic acid, 6 per cent After bagasse is crushed or cut up and ground, it is being used for making insulating and acoustic board and refractory brick Bagasse is composed of fiber, about 1 per cent protein and 3 to 4 per cent silica Workers who are exposed to massive amounts of bagasse dust in connection with its handling, shipping or manufacturing processes, may develop this disease The length of exposure sufficient to cause pulmonary involvement varies from three weeks to two years It is likely that the expanding industrial uses of bagasse and the awareness of its disease causing potentialities, will reveal a larger number of cases than reported hitherto

Various concepts have been proposed as to the actual pathogenesis of bagasse disease Aspergillus fumigatus, one of the mold like fungi, has been isolated from bagasse Also, in experimental animals (chicks rabbits, guinea pigs) pulmonary disease was produced by bagasse and subsequently, Aspergillus fumigatus was recovered from the lung lesion The experimental studies of Gerstle and his co-workers support the assumption that a fungus is the cause of the disease Schneiter and his coworkers advanced the view that Aerobacter cloacae should be considered as a possible etiologic factor in bagasse disease They were able to isolate this micro-organism in high percentage of samples of fresh bagasse, aged bagasse, processed bagasse, mill dust, mill air and sawdust from bagasse fiber board Hunter and Perry were able to isolate twenty different species of fungi from bagasse dust Even so, on the basis of his meticulous studies, Sodeman emphasized the point that no fungus has been consistently isolated in human cases of bagasse disease and that there is as yet little evidence of fungus as a causative agent X ray diffraction analysis of the ash of bagasse shows from 3 to 4 per cent silica This in itself is insufficient to explain the pathologic changes in the lung Castleden and Hamilton Paterson found that whole bagasse contains a protein which is soluble in isotonic solution of sodium chloride They expounded the possibility of bagasse disease developing in persons as the

result of allergy to this substance Sodeman and Pullen demonstrated by aspiration biopsy as well as on postmortem examination, that spicules of bagasse, which rotate polarized light, are deposited in the lungs of these patients as far down as the alveoli

Symptoms

The usual chief complaint of individuals with bagasse disease are dyspnea and cough The dsypnea may be so severe that it forces the patient to bed Dyspnea may be associated with retrosternal pain The cough is moderate or severe The sputum is scanty and mucoid, in some cases, it is mucopurulent, greenish-yellow and foul smelling There are no eosinophil cells in the sputum Blood streaked expectoration or occasionally, as much as a drachm of blood a day in the sputum may occur Fever, usually intermittent, ranging to 102° to 104°F, persists from a few days to two to three months Chills and night sweats are common In other instances, fever is entirely absent Cyanosis, great weakness and mental depression have also been reported during the acute phase. Sodeman expressed the view that milder cases of bagasse disease, with x ray findings but without disturbing symptoms are likely to occur in persons exposed to the dust of bagasse Possibly, future industrial surveys will corroborate this assumption

Diagnosis

Physical findings over the chest may be irrelevant, or signs of consolidation are found and fine moist rales are detectable over the upper or lower one half or entire extent of one or both lungs In patients with severe dyspnea, there are retraction of muscles over the upper thoracic region and also, noticeable hyperactivity of the accessory respiratory muscles The roentgenogram of the chest reveals a uniform punctate infiltration or miliary mottling or areas of bronchopneumonic patches in both lung fields Clearing of the roentgenologic findings ensues in from one to six months In some patients, residual pulmonary fibrosis is visualized after clinical recovery The blood shows leucocytosis which may reach 20,000 per cm, with an increase in the polymorphonuclear cells The sedimentation rate of the erythrocytes is accelerated In the differential diagnosis, it is important to rule out tuberculosis, typhoid and paratyphoid fever, tularemia, brucellosis, Loeffler's syndrome, bronchopneumonia of bacterial, rickettsial or viral origin, fungus infection, infestation with animal parasites and pulmonary lesions of nodular

character on the x-ray film These are enumerated in the chapter on *Pulmonary Manifestations of Collagen Disease* Lemone and his associates emphasized the reversibility and complete disappearance of roentgenologic changes in the lung with bagassosis in contrast to the permanent pulmonary lesions in silicosis

It has been shown that bagasse disease is preventable. In collecting bagasse, and at manufacturing plants, the dust count of the atmosphere can be effectively reduced by exhaust ventilation, or by the use of water spray

Treatment

The treatment consists of bed rest and symptomatic and supportive measures In a group of 24 patients with bagasse disease Hunter and Perry recorded a mortality rate of eight per cent

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PULMONARY DISEASES CAUSED BY NOXIOUS GASES FUMES AND DUSTS

By ANDREW L BANYAI, M D and J WINTHROP PEABODY, M D

Discussion of this subject deserves special attention on account of the possibilities of exposure through a great many industrial processes also, because of past war experiences and foreseeable potential dangers of future warfares On the basis of empirical knowledge and pertinent experimental studies, a great deal of information has become available for practical clinical and preventive applications We intend to present the salient aspects of this problem On account of the technical limitations of the text, the discussion will be confined to the most important items Other closely related topics, such as fungus infections exposure to silica asbestos other silicates and other dusts capable of causing pulmonary damage are presented in the respective chapters For the discussion of bronchial asthma caused by vegetable dusts, chemicals and other substances, the reader is referred to the chapters on Bronchial Asthma Also, the carcinogenic properties of radioactive emanations are discussed under separate heading

Acetone (CH_3 CO CH_3) is a widely used solvent in industries which produce acetate, acetylene celluloid, lacquer, nitrocellulose and silk It has a pleasant odor and a pungent taste Inhalation of its vapors in large amounts is followed by bronchitis Also, it has a general narcotic effect

Acrolein (CH_2 CHCHO) is a colorless liquid of pungent odor The inhalation of its vapors in large amounts is bound to cause a more or less severe bronchitis The symptoms are typical of this condition Exposure to acrolein occurs in the manufacture of soap, stearic acid varnish, oil cloth, linoleum, bone and tallow rendering

Allyl Chloride (CH_2 $CHCH_2Cl$) has been found to be one of the most toxic halogenated aliphatic hydrocarbons by Adams and his associates Experimental exposure of animals to concentrations of 100, 50, 20 and 10 mg per liter of the vapors of this chemical caused pathologic changes in the lung, characterized by congestion, interstitial edema frequent hemorrhage and varying degrees of exudation into the alveoli and congestion, thickening and desquamation of the mucous membrane of the bronchioles The principle cause of death was injury to the lung

Ammonia (NH_3) is a well known gas which when inhaled in large quantities, causes bronchitis, bronchopneumonia or both The accom

panying cough is severe and paroxysmal in character It is productive of tenacious, mucoid or mucopurulent sputum that is occasionally blood tinged According to the findings of Cralley, the ciliary activity of the respiratory mucous membrane ceases when the concentration of ammonia in the inhaled air is 400 parts per million or over Severe exposure to this gas is likely to cause pulmonary edema It is well to keep in mind that sudden death may result from the inhalation of ammonia It is brought about by reflex cessation of respiration Ammonia is used in the manufacture of carbonate of soda bone black, varnish, lacquer, beet sugar and in the production of ice Exposure to this gas may take place in refrigeration plants, frozen food lockers, near coke ovens, in handling ammonia cylinders, in industries engaged in tanning mirror-silver production, metal plate coating and in miscellaneous chemical plants Also, men working in sewers are exposed to ammonia. Goshorn reviewed various adsorbents used for filling canisters for ammonia masks He noted that the most efficient adsorbents were kupramite which is copper sulfate crystallized on pumice, cobaltous chloride hexahydrate impregnated pumice, silica gel and pumice impregnated with 40 to 50 per cent of acids, such as oxalic and phosphoric Charcoal impregnated with weak acids serves the same purpose Goshorn remarks that the first two are very efficient but lose water of crystallization rapidly on exposure to atmospheric conditions, and form salts which are poor ammonia adsorbents Silica gel tends to evolve ammonia subsequent to exposure to the gas

Ammonium Picrate ($C_6H_2(NO_2)_3ONH_4$), an orange colored crystalline substance, is an explosive which is used as a bursting charge in armor piercing shells Individuals engaged in the processing and handling of this compound are known to have developed sensitization dermatitis Sunderman and his associates surveyed a group of 71 workers exposed to ammonium picrate dust Most of them complained of tight feeling in the chest, a sharp taste or an odor in the back part of their noses Experiments conducted by these investigators revealed that keeping animals in cages in the buildings where milling and performing operations of ammonium picrate were done, for from six weeks to twelve months, caused congestion of the trachea, acute catarrhal tracheitis and extensive destruction of the mucosa of the bronchi

Amyl Acetate ($CH_3COO\,C_5H_{11}$) has a great variety of industrial uses as a solvent for fats, nitrocellulose, oils and resins Inhalation of its vapors is bound to cause bronchitis and bronchopneumonia in addition

to headache, dizziness, malaise, drowsiness, palpitation and gastrointestinal disturbances

Antimony Trioxide The potential toxicity of antimony trioxide (Sb_2O_3) was studied experimentally by Dernehl and his associates Animals were placed in an exposure chamber, the atmosphere of which contained 45 4 mg of this compound per cubic meter of air The total amounts inhaled by each animal varied from 13 to 424 mg of antimony trioxide All developed pathologic changes in the lung Histologic examination showed

1 Uniform thickening of the alveolar walls, such as found in interstitial pneumonitis,

2 Hypertrophy of the pulmonary lymphoid tissue, such as occurs with any dust exposure,

3 Particles of antimony trioxide in phagocytes in the interstitial spaces,

4 Filling of the alveoli with edema fluid in areas where there was as yet, no pneumonitis The train of events in the development of these conditions was portrayed by these investigators as follows The inhaled dust causes the liberation of edema fluid in the alveoli Phagocytes enter the edema fluid, ingest some of the dust particles and then return to the interstitial tissues of the alveoli where the majority of them die causing the liberation of toxic antimony The latter provokes interstitial pneumonitis

Arsenic Trioxide (As_2O_3) and *Arsenous Chloride* ($AsCl_3$) are inhaled in the form of dust or gas in connection with the manufacture of arsenic colors, dyes, colored chalk, glass, oil cloth, artificial flowers and items used in fireworks Also, exposure to these compounds is known to exist in the mining of arsenic, taxidermy, textile printing and dyeing Various degrees of bronchitis result from such exposure

Barium Carbonate ($BaCO_3$) is used in metal finishing processes When it is melted between electrodes for this purpose, its fumes may be inhaled Such inhalations are followed by stubborn bronchial irritation

Bromine and Hydrogen Bromide Fumes of bromine and hydrogen bromide (HBr), when inhaled in large quantities, are likely to cause severe bronchitis or pulmonary edema

Methyl Bromide (CH_3Br) is a useful fumigant and serves as intermediate in chemical manufacture Also, it has been used for refrigeration and it is considered the most effective fire extinguishing medium against gasoline fires on airplanes, tanks and motorized equipment It

represents a definite health hazard when its vapors are inhaled in large amounts The experimental studies of Irish and his associates revealed that animals exposed to the vapors of this compound in high concentrations, develop lung irritation Examination of pathologic specimens showed moderate to pronounced congestion of this organ Postmortem findings in human subjects were described by Duvoir and Derobert The lungs showed widespread emphysema and extensive leucocytic infiltration, with or without moderate pulmonary edema The edema fluid contained many erythrocytes, polymorphonuclear leucocytes, and necrotic alveolar epithelial cells with large, brown, refractile cytoplasmic inclusions Clinically the inhalation of the vapors of methyl bromide results in symptoms which closely resemble an acute head cold and may be associated with protracted cough and mucopurulent sputum Concurrent manifestations may include headache, dizziness, nausea, vomiting, general muscular weakness, muscle twitching, paresthesias, drowsiness, fever, convulsions and coma Fatal termination may ensue in 48 hours due to asphyxia caused by pulmonary edema

Cadmium Oxide (CdO) is bound to lead to the development of serious pulmonary damage when there is long or intense exposure to its fumes or dust Cadmium is extensively used in alloys, dyeing, neutron absorbers, photography, electroplating, waterproofing, alkaline storage batteries, ceramics, making electric conductors, jewelry, plating pigment and in the manufacture of cadmium faced bearings Accidentally, harmful exposure may exist in cadmium smelters and in connection with melting, welding, spraying and plating Prodan found peribronchial and perivascular fibrosis in experimental animals following the inhalation of cadmium oxide These findings were confirmed by Paterson Also, he noted acute pulmonary edema that develops in experimental animals within 24 hours of exposure and reaches its peak within three days When the animal survived, proliferative interstitial pneumonitis was noted that lasted from the third to the tenth day after exposure As part of the proliferative process, epithelization of the alveoli occurs which interferes with the normal respiratory gas exchange, but subsequently, it disappears The experimental observations of Harrison and his associates revealed the following findings after the inhalation of *cadmium chloride* ($CdCl_2$)

Extensive pulmonary edema, necrosis of the lining epithelium of the lower respiratory tract, particularly of the respiratory bronchioles, together with the destruction of the bronchiolar smooth muscles These

changes are associated with the formation of polymorphonuclear exudate within the bronchi and bronchioles, obstructive organization, secondary atelectasis and emphysema The latter, together with the fibrosis persisted and emphysematous bullae were noted Bacterial pneumonia may complicate the picture It is reasonable to assume that similar pathologic conditions develop in man after prolonged exposure to concentration of cadmium salts which cause no acute symptoms In fatal human cases, postmortem examination showed catarrhal bronchitis edema, congestion and hemorrhage in the lung, partial atelectasis and proliferative interstitial pneumonitis Barrett and his associates found the cadmium oxide content of the lung in two men who died after industrial exposure 1 7 and 1 8 mg per 100 Gm of dry tissue. Cadmium oxide particles can be visualized in microscopic sections by the method of Thiers and his associates Barrett and Card calculated that the lethal dose of cadmium oxide for man is not over 2,900 min mg per cubic meter and possibly as little as half of this value for arc produced fume On the basis of his animal experiments, Paterson considered concentration of cadmium oxide of 0 1 mg per cubic meter of factory air (representing a cumulative dose of 50 min mg per cubic meter for an eight hour day) an adequate margin of safety The following symptoms have been observed after massive exposure sudden onset of severe persistent cough, feeling of oppression and constriction in the chest, intense chest pain, dyspnea, dryness in the throat, nausea and vomiting X ray examination of the lung reveals patchy bronchopneumonia and widespread pneumonitis As to the treatment of this condition the studies of Harrison and his associates offer a valuable pointer They noted beneficial therapeutic results in dogs from the intravenous or intramuscular injection of BAL (2 3 dimercaptopropanol) given as soon as possible after exposure, in large doses that is, 60 mg per Kg of body weight, during the first four hours, in three divided doses

Carbon Tetrachloride Carbon tetrachloride (CCl_4) is an excellent solvent for fats, oils and tar and for this reason, it is widely used in industry Exposure to it may be hazardous in three ways

1 It may cause severe toxic nephrosis

2 When heated to high temperature, phosgene and hydrochloric acid develop from it

3 Inhalation of its fumes in excessive amounts causes direct pulmonary damage Thompson reported a number of cases belonging to the latter category which occurred in Naval personnel on a submarine.

Postmortem findings in one of these cases were extensive consolidation of both lungs, with a dark red cut surface and purplish red bronchial mucosa Microscopically, it was noted that there were pronounced venous capillary congestion and edema The alveoli were filled with granulocytes, numerous erythrocytes and many swollen, lightly pigmented macrophages.

Symptoms which followed exposure include anorexia vomiting, hematemesis, bloating, general muscular pain, prostration generalized waxy edema, oliguria, with other signs of nephrosis Only one out of 20 patients presented pulmonary symptoms In this case, acute respiratory distress was noted, with red, frothy sputum, deep cyanosis, rapid respirations, increased pulse rate and normal temperature There were two types of roentgenologic findings

1 In the fatal case, consolidation of all five lobes was noted

2 In patients who had no complaints or signs referable to the lung, roentgenograms of the chest showed enlarged hilar shadows and an increase in the bronchovascular markings spreading from the root of the lung to the periphery These changes cleared in three days Contrary to prevailing standards, Elkins maintains on the basis of personal investigations, that 100 parts per million as the maximum allowable concentration of carbon tetrachloride in the atmosphere is too high and that the safe value is not above 50 p p m

As to treatment, in addition to measures aimed at alleviating the pulmonary condition, the patient is given repeated large loses of calcium until complete recovery takes place

Chlorine is a pungent greenish gas and a well known irritant of the respiratory tract Exposure to it may occur in its production and in the manufacture of its organic and inorganic compounds, also in its use as a disinfectant and bleaching agent According to the observations of Cralley cessation of the ciliary function of the mucosa of the respiratory tract sets in when the concentration of chlorine reaches 30 parts per million Inhalation of chlorine in concentration of 1 10,000 causes spasm of the bronchial smooth muscles, exudation and consequent bronchial occlusion Higher concentrations lead to tracheobronchial and pulmonary edema and bronchopneumonia The edema is usually noticeable throughout both lungs but in some cases it may be localized in the bases Massive exposure is likely to cause immediate death In individuals who survived excessive exposure Gilchrist and Matz reported residual changes in the lung in 10 per cent

Symptoms which follow the inhalation of chlorine include severe cough, expectoration of yellow, serous fluid, pain in the chest, which may be substernal, dyspnea, cyanosis, pulmonary hemorrhage, spasm of the glottis, headache, dizziness, sweating and vomiting. Dyspnea is brought about by occlusion of the bronchi, edematous filling of the alveoli, loss of plasma through the formation of pulmonary edema and circulatory failure due to increased pulmonary resistance.

Roentgenograms of the chest show irregular mottling of varying densities and changes suggestive of bronchopneumonia. The course of the latter is frequently benign. Its development, if anticipated, can be prevented by prophylactic administration of penicillin intramuscularly or in the form of inhalations. Chasis and his associates prefer sulfadiazine medication for the same purpose. When exposure to chlorine is not too great, symptoms of bronchitis subside in a week or sooner, also, dyspnea and substernal pain disappear within a few days.

Pulmonary edema is treated according to principles outlined in the respective chapter. Cases of severe bronchitis derive substantial benefits from the intravenous or oral administration of theophyllline with ethylen ediamin (aminophyllin). The latter is effective through its broncho dilator influence. Its clinical use is advocated for the reason that the lung tissue contains appreciable amounts of histamine which when liberated from its sources by chemical irritation, causes spasm of the bronchial smooth muscles. Also, it is of advantage to give the patient 0.5 or 1 cubic centimeter of 1:100 solution of neosynephrin or the same amount of 1:100 solution of epinephrine in aerosolized form in instances where bronchospasm is thought to be present. Arloing and his associates commented on the effect of chronic chlorine poisoning on tuberculosis. Their experimental investigations revealed that in guinea pigs exposed to prolonged inhalations of light concentrations of chlorine before and after infection with tubercle bacilli, chronic chlorine poisoning favors the development of tuberculosis.

Chloropicrin. Chloropicrin (nitrochloroform) $(Cl_3C\,NO_2)$, one of the recognized war gases, is a sweetish chemical which has a flypaper odor. Its massive inhalation is followed by pulmonary edema. It is one fourth as toxic as phosgene.

Chromium Compounds. The dust of chromium compounds when inhaled in large amounts, causes bronchitis or bronchopneumonia. These compounds are widely used in various chemical and industrial processes, including the manufacture of metal products, dye industry photo

graphy, textile printing and others. Brinton and his collaborators report that the incidence of carcinoma of the respiratory system is 29 times greater in chromate workers than in the general population.

Cotton Dust. Neal and his associates reported the occurrence of an acute respiratory disease in workers engaged in mattress making or employed in cotton mills and cotton seed processing plants, after exposure to cotton dust from low grade, "stained," cotton. The disease is attributed to the endotoxins of the Aerobacter cloacae commonly found in the soil. Respiratory symptoms may develop after a brief exposure, from 1½ to three hours and lasts from one to two days. The symptoms are: Cough, tightness in the chest, dyspnea, dryness in the throat, brassy voice, sneezing chills, moderate fever, generalized aches and pains, malaise, anorexia, nausea, vomiting, diarrhea, abdominal discomfort, nervous irritability, vertigo and insomnia. There is considerable leucocytosis in these cases. The disease is preventable by wearing protective respirators.

Diazomethane (CH_2N_2) is a yellow gas used in the chemical industry. It is capable of causing severe, necrotic bronchitis, bronchopneumonia and pulmonary edema.

Dimethylsulfate ($[CH_3]_2 SO_4$) is a colorless liquid used in the chemical industry for methylation, also, for general laboratory purposes. The harmful effect of the inhalation of its vapors is attributable to its decomposition in the lung into sulphuric acid and methyl alcohol. Consequently pneumonia, pulmonary edema and hemorrhages develop with corresponding clinical manifestations. The pulmonary pathologic changes are usually associated with cramps or paralysis of the muscles and stupor. Severe poisoning carries a high fatality rate.

Ethyl Acetate ($CH_3COOC_2H_5$) is a very volatile liquid with pleasant odor and pungent taste. In the chemical industry it is used for synthetic purposes. Also, it is often added to fruit essences, perfumes, vinegar and wine. Repeated heavy inhalations of its vapors results in bronchitis or in pulmonary edema.

Ethyl Acrylate ($CHC_2{=}HCOOC_2H_5$) is a liquid used in the production of resins. The toxicologic properties of this compound were first studied by Pozzani and his associates. In their animal experiments, they noted that inhalations of high concentrations of ethyl acrylate results in severe pulmonary congestion and hemorrhage. Pneumonic involvement was induced when the concentration of ethyl acrylate in the inhaled air was 540 parts per million. The damaging effect of this compound

upon the lung is greater than that of methyl acrylates Pozzani and his associates conclude that the hygienic standard for repeated human exposure to ethyl acrylate vapors should not be above 50 million particles per million

Ethylamines Monoethylamine ($C_2H_5NH_2$), diethylamine [$(C_2H_5)_2NH$] and triethylamine [$(C_2H_5)_3N$] are widely used in paper manufacturing, and in the chemical and rubber industries The experimental studies of Brieger and Hodes revealed pulmonary irritation in animals exposed to 50 parts per million of any one of the three compounds The pathologic findings were hyperemia, small hemorrhages, peribronchitis bronchopneumonia, and thickening of the vascular walls

Ethylene Chlorohydrin ($CH_2OH \cdot CH_2Cl$) is a well known solvent for acetyl cellulose, dyes, lacquers, resins and wax Also, it is used as a detergent and in the manufacture of oilcloth Severe poisoning by its vapors is followed by pronounced congestion of the mucosa of the respiratory tract and by pulmonary edema Cases of death attributed to poisoning by inhalation of ethylene chlorohydrin vapors have been reported In some instances, hemorrhages into the pleural cavity were found on necropsy

Fluorine and Hydrogen Fluoride (HFl) are irritants to the respiratory tract Their inhalation is followed by bronchitis or pulmonary edema Exposure to these gases may occur in connection with a number of industrial processes, such as glass, pottery, aluminum, beryllium and magnesium production, oil refining and others

Formaldehyde (HCHO) is used in the manufacture of plastics and other industrial processes When its concentration reaches 20 parts per million in the inhaled air, exposure during a single day may result in bronchitis with severe cough pulmonary hemorrhage emphysema and a predisposition to secondary pyogenic infection of the lung with abscess formation Experimentally it was noted by Cralley that ciliary motion of the respiratory mucosa ceases when the concentration of formaldehyde is 30 parts per million or over

Hydrochloric Acid (HCl) is a colorless substance extensively used in the chemical and rubber industry metallurgy, pottery, glass manufacturing and in the production of fertilizers Inhalations of its fumes leads to the development of bronchitis and, in severe cases, to pulmonary edema According to Kober and Hayhurst, a concentration of 0 05 per mille of hydrochloric acid in the air is well borne for a short time This is in harmony with the observations of Machle and his associates

who found neither immediate toxic effect nor late pathologic changes resulting from exposure of experimental animals to 0 05 mg of hydrochloric acid per liter of air, six hours a day, five days a week, for four weeks On the other hand, higher concentrations of this compound produced severe inflammatory reaction with edema and necrosis in the tracheal and bronchial mucosa and in the alveoli The pulmonary blood vessels were edematous and showed necrosis of the intima and media, with resultant thrombosis and infarction In addition, there was evidence of extensive pulmonary edema, atelectasis, emphysema, confluent bronchopneumonia and frequently, large and small abscesses. Animals which survived exposure to higher concentrations of hydrochloric acid from five days to one month showed a perivascular and peribronchial fibrosis besides emphysema, atelectasis and purulent bronchitis Similar changes were noted in animals which survived 18 months following exposure In some of these, bronchopneumonia and lung abscess were present Long exposure to concentrations less than 1 mg per liter did not cause serious damage to the lung in guinea pigs The pathologic changes consisted of mild bronchitis and peribronchial fibrosis In rabbits, however, the same exposure frequently led to bronchopneumonia and lung abscess

Gasoline (C_6H_{14} $C_{12}H_{26}$) is not only a well known industrial solvent but also the most widely used source of energy for transportation Pulmonary lesions may develop following massive inhalation of its fumes and also, after its aspiration or ingestion In the latter instance, pathologic changes in the lung are brought about by the elimination of gasoline through the lung Regardless of whether gasoline is reaching the lung by direct inhalation, aspiration or through the blood stream, the local response is either pulmonary edema or an acute or prolonged necrotic, hemorrhagic inflammatory lesion At the same time, manifestations on the part of the central nervous system are noted, such as a brief period of animation, euphoria excitement and tremor These are followed by sudden drowsiness and deep coma Death may occur early as the result of paralysis of the respiratory center

Inhalation of a mixture of 5 per cent carbon dioxide and 95 per cent oxygen is the best means for the rapid elimination of gasoline from the body This treatment is not to be given to patients with acute plastic pleurisy or marked hypertension Castex and his associates reported the case of a man who aspirated half a glassful of gasoline The most conspicuous findings were vomiting, cough, severe chest pain, pulmonary

edema, atelectasis of the middle and lower lobes and leucocytosis Atelectasis was attributed to bronchial occlusion by inflammatory exudation The intense chest pain was explained on the basis of experimental observations which showed that gasoline aspirated had a tendency to reach the subpleural zone The ensuing inflammatory reaction involves the overlying pleura with its rich sensory nerve supply When gasoline was instilled through the nose of animals, these investigators found intense pulmonary congestion, edema, broncho alveolitis, necrotic foci in the alveolar and peribronchial tissues, atelectasis around these foci and bronchopneumonia If the animals lived long enough, fibrosis developed around the affected alveoli, bronchi and atelectatic areas

In this connection, a report of Crisci and his associates can be mentioned By mistake, two of their patients were given intravenous injection of 4 5 and 10 cc of kerosene, respectively Toxic alveolitis resulted which was associated with severe cough, blackish expectoration feeling of suffocation fever and mental confusion Roentgenograms of the chest showed large miliary nodules in both lungs Also, serosanguineous pleural effusion was observed in one of these patients Toxic symptoms disappeared in two weeks Scott reported unusual pleuropulmonary sequels to ingestion of kerosene In a boy aged two years pneumonia, bilateral pneumothorax and subcutaneous emphysema followed the ingestion of one to two ounces of kerosene The child completely recovered on general supportive measures and sulfathiazole therapy

Olstad and Lord studied the roentgenograms of the chest in 44 children who accidentally ingested kerosene Twenty six (59 per cent) had evidence of pneumonia Prompt removal of the ingested kerosene with copious gastric lavage was found helpful in reducing the incidence of pneumonia

"Grain Fever" Grain handlers may develop respiratory symptoms as a manifestation of an occupational disease, as reported by Smith and his associates The complaints of such individuals are attributed to insecticides frequently used for the treatment of grain transported in boats and also, to "grain fever" The insecticides implicated are carbon tetrachloride and sulphur dioxide These may cause sneezing dryness and burning of the nose, burning sensation in the eyes dryness and burning in the throat and in the chest, dyspnea, cough, vertigo, headache nausea, vomiting and burning of the skin The so called grain fever is similar to metal fume fever It is characterized by general malaise, aches and pains, with chilly and feverish sensations about two to three

hours after a day's work Physical examination reveals impaired percussion note, diminished or harsh breath sound and moist or sonorous rales These investigators found x ray evidence of pulmonary fibrosis in 2 3 per cent of their cases and non-specific lung infection in 1 8 per cent

"Thresher's Lung" is pulmonary moniliasis See chapter on *Fungus Diseases*

Hydrogen Cyanide Gas (HCN) is one of the most rapidly acting toxic substances It is highly volatile, penetrating and has a faint odor resembling that of bitter almonds It is widely used in fumigation Its harmful effect on the human body is primarily due to its capacity to act as a cell poison which inhibits oxidation Inasmuch as nerve tissue is highly susceptible to the action of hydrogen cyanide, paralysis of the respiratory center in the medulla readily ensues following severe exposure The lethal dose for an adult is from 50 to 70 mg According to Gettler and St George in cases where death follows the inhalation of cyanide gas, there are swelling and edema of the mucous membrance of the respiratory tract, with ecchymosis and hemorrhages and also, with pulmonary congestion and edema

The essential points of treatment are

1 Maintenance of respiration and circulation To this end, one should resort to the inhalation of 5 per cent carbon dioxide with 95 per cent oxygen or to artificial respiration

2 Inhalation of amyl nitrite for from 15 to 30 seconds to two to three minutes

3 Intravenous injection of sodium nitrite Five grains (0 3 Gm) of the drug are dissolved in 10 cc of water and injected in two minutes

4 Sodium thiosulphate is given intravenously in the form of 5 per cent solution of which from 25 to 500 cc is to be administered The antidotes are repeated in from one to two hours, if necessary

5 Gastric lavage is done when hydrogen cyanide has been ingested

Hydrogen Sulfide (H_2S) is well known as an industrial hazard on account of its effect upon the central nervous system Less familiar is the fact that high concentrations of this gas may cause pulmonary damage, including edema Immediate death may result from respiratory paralysis Exposure to hydrogen sulfide may occur in oil refining, tanning manufacture of viscose material, gypsum and sulphur mines, caisson work and through exposure to industrial waste and sewage gases

In addition to general supportive measures, patients with hydrogen

sulfide intoxication are treated with carbon dioxide — oxygen inhalations and by intravenous injections of methylene blue, 50 cc of a 1 per cent solution, to a total of 200 cc in repeated doses if circumstances require Also, satisfactory results are obtained from the intravenous injection of sodium thiosulfate The initial dose is 20 cc of a 5 per cent solution This may be increased to 100 cc if necessary and repeated from four to five times during the first 24 hour period

Isophorone ($CO[CH\ C\ (CH_3)_2]_2$) is an unsaturated cyclic ketone, with a distinct odor It is markedly irritating to the conjunctiva and the mucous membrane of the respiratory tract It is an excellent solvent for many oils, gums and resins On account of this property, it is used as a vehicle for lacquers and other surface coatings Its toxicity was investigated experimentally by *Smyth* and *Seaton* Exposure of animals to various concentrations of the vapors of this compound resulted in pathologic changes in the lung kidney heart liver and spleen, with frequency of involvement in this order The pulmonary findings consisted of general congestion, filling of the alveoli and bronchioles with secretions, red blood cells and desquamated epithelial cells Secondary pneumonia was detected in 5 per cent of the cases

Iron Compounds Iron alloys containing iron silicate and iron manganese silicate have been noted to provoke certain toxic effects during processing It is the consensus that bronchitis encountered in workers exposed to the dust of these alloys for an extended period of time is most likely due to impurities in the form of phosphene (PH_3) and arsene (AsH_3)

Isovaleraldehyde (2 methylbutiraldehyde) ($[CH_3]_2CHCH_2CHO$) Wilkinson reports the occurrence of poisoning in men exposed to the vapors of this compound for several hours Their complaints were tightness in the chest, irritation of the respiratory tract, headache, anorexia nausea vomiting and weakness One of his patients showed evidence of spontaneous pneumothorax

Lewisite (chlorvinyl dichlorarsine) ($ClCH\ CHAsCl_2$) is a heavy, volatile, oily fluid primarily known as a vesicant Its odor is similar to that of geranium When its fumes are inhaled, they act as lung irritants

[illegible]

in the glass and pottery industries Moreover, manganese to po[illegible]

are used in anti rust coatings, clarifiers, disinfectants, fluxes, germicides, preservatives and pyrotechnical products Also, manganese poisoning occurs in miners of this ore who are working unprotected from massive dust exposure Manganese oxide (MnO_2) is a brown substance It exerts its damaging effect on the lung when inhaled in large amounts in connection with certain chemical production processes and also, after exposure to the dust of basic slag from which manganese is secured This basic slag contains 10 per cent manganese dioxide

Gundel and Fischer reported that 2 per cent of basic slag workers died of pneumonia Joetten and his associates cite a report from a small community in Norway, located in a valley where in a plant, manganese compounds were smelted Fumes resulting from this process filled the atmosphere of the valley Records show that of the entire population of this town, 32 per thousand died of pneumonia The pneumonia death rate was 4 per thousand population for Norway during the same period Expressed in other terms, one third of all deaths was due to pneumonia in this community Davies noted an incidence of pneumonitis 26 per thousand in men exposed to manganese dioxide in a plant manufacturing potassium permanganate This compared with 0 73 per thousand in nonexposed controls He found that from 41 to 66 per cent of the dust in the atmosphere was manganese dioxide, practically all particles less than one micron in size

Individuals with manganese pneumonitis develop the disease suddenly, with considerable cough, pain in the chest, dyspnea or asthma like symptoms Physical examination of the chest reveals moist rales and sonorous and sibilant rales The roentgenograms of the chest show accentuation of the bronchovascular markings, with hazy outlines and a generalized fluffiness as in pulmonary edema As a complication, areas of segmental or lobar consolidation are noted In patients with predominantly asthma like symptoms, increased bronchovascular markings are in evidence These patients respond to penicillin or sulfonamides less favorably than ordinary cases of pneumonia Davies observed that with the clinical recovery of the patient, the roentgenologic changes completely disappear In general, without pneumonia, and with pneumonia of limited extent, the prognosis is favorable

Animal experiments carried out by Davies with the inhalation of dust containing 70 per cent manganese dioxide are very illuminating in this regard The description of his findings may be summarized in the following

1 Pathologic changes were dependent on the length of exposure

2 There were slight or marked mononuclear interstitial infiltrations together with many dust laden cells, and consolidation These changes were particularly prevalent around the bronchi

3 Edema of the alveolar and bronchial epithelium was visible

4 In addition to the interstitial spaces, the alveoli were also packed with large mononuclear cells

5 Areas of necrosis were frequent

6 Dust laden cells were relatively few in number but were observed in the bronchi, alveoli and interstitial tissue Their paucity is attributed to the solubility of manganese dioxide in cellular fluids, which is followed by destruction of the phagocytic elements

Methacrylates The potential toxic properties of methacrylates (CH_2 $CHCOOCH_3$) were investigated by Deichmann in view of the wide application of the polymerized forms of these compounds as the intermediary layer in safety glass, as electrical insulating agents, coatings on rubber, glass and textile and for making light conducting rods for indirect lighting and cold light Also, these compounds are used in making lenses magnifying glasses, goggles and windows and windshields in aircraft

When experimental animals inhaled various concentrations of methyl ethyl and n butyl methacrylates, Deichmann noted that the trachea bronchi and the lung parenchyma were greatly congested, edematous with scattered small areas of hemorrhages and emphysema An initial increase in the respiratory rate was followed by decreased respiration dyspnea and death from respiratory failure There was a concurrent elevation of the porphyrin content of the blood

Methyl Alcohol (wood alcohol) (CH_3OH) is a colorless fluid the vapors of which may cause severe bronchitis and bronchiolitis and after massive exposure, pulmonary edema or paralysis of the respiratory muscles Exposure to the vapors of methyl alcohol occurs in its production, also, in its use in the chemical and pharmaceutical industries, as a solvent of lacquers, mordants, polishes, moreover, as a denaturing agent for industrial alcohol and for numerous other purposes

Monomeric Styrene (phenyl ethylene) (C_6H_5CH CH_2) is used in large quantities for the manufacture of plastics and synthetic rubber Its toxicologic properties were investigated by Spencer and his associates in experimental animals The degree of pulmonary damage varied with the vapor concentration and with the length of exposure and included slight, moderate or severe congestion, hemorrhages, edema, exudation

and leucocytic infiltration When immediate death did not result from the exposure, in many of the animals fatal pneumonia followed the initial lung irritation Spencer and his associates consider 2 mg per liter (400 parts per million), which gives a disagreeable odor, as permissible limit for repeated exposure of industrial workers

Mustard Gas [$(Cl\,CH_2CH_2)_2S$] is one of the notorious implements of modern, shall we say, civilized warfare In addition to combatants, arsenal workers loading shells with this gas are liable to suffer from exposure to it Chemically, mustard gas is dichlordiethyl sulfide In spite of its suggestive name, it is not related chemically to genuine mustard oil, although its odor resembles that of these oils, horseradish and garlic Mustard gas is known to be lethal in concentrations varying from 0 006 to 0 2 mg per liter Its deleterious effect is predicated on the intensity and length of exposure and on individual susceptibility Half an hour inhalation of this gas in concentration of 0 07 mg per liter is considered lethal The following pathologic changes were recorded In persons who died within 48 hours after exposure in World War I, there was a false membrane which covered the inner surface of the trachea, bronchi and bronchioles In those who died after 48 hours, in addition to these changes, the lung showed necrotizing bronchopneumonia with abscess In moderately severe industrial exposure, one can anticipate inflammatory changes of the respiratory mucous membrane, with edema, necrosis loss of cilia, destruction of the elastic fibers and bronchiectasis Bronchopneumonia resulting from secondary bacterial invasion is a frequent complication Casualties due to this cause in the first world war were found to have respiratory symptoms such as dryness of the throat, hoarseness severe brassy cough, yellowish expectoration, dyspnea, soreness and constriction in the chest, photophobia and lacrimation Protracted, light industrial exposure leads to huskiness of voice, hacking, paroxysmal cough with expectoration of mucoid or mucopurulent sputum, some times as much as 16 ounces in 24 hours, tightness in the chest, or retrosternal pain, wheezing and dyspnea Sometimes, the sputum is blood tinged and rarely, the patient has frank pulmonary hemorrhage Also, one finds irritation of the mucosa of the eyes, nose bleeds, loss of smell and occasionally, headache, loss of taste, anorexia, difficulty in swallowing, constipation or diarrhea, weakness, nervous irritability and insomnia Low grade fever is often seen and in some instances, loss of weight In industrial plants, it may take from three weeks' to two years

exposure before symptoms become manifest On the other hand, massive inhalation of mustard gas results in immediate shock and collapse

In the average case of mustard gas poisoning, physical examination of the chest reveals sonorous and sibilant rales and occasionally, coarse moist rales throughout both lungs There are instances, however, where no abnormal physical findings are detected In chronic forms, pathologic changes may be aggravated or alleviated by changing atmospheric conditions The roentgenogram of the chest may appear normal in uncomplicated cases In others, basal interstitial fibrosis and emphysema are noticeable Following massive exposure, bronchopneumonia and occasionally, abscess are visualized Morgenstern and his associates report the occurrence of bronchographically demonstrable bronchiectasis following chronic exposure in plants in 52 per cent of persons who developed chest symptoms Also, they noted peribronchial patchy atelectasis in these individuals Bronchoscopic examination showed mucosal congestion and edema in the bronchi

Relative to prognosis in persons with pulmonary disease due to exposure to mustard gas, spontaneous improvement in the symptoms is rare As a matter of fact, some of these individuals become permanently partially disabled on account of chronic bronchitis with associated respiratory insufficiency Patients who suffered a massive exposure, such as war casualties, are removed on a stretcher and put to bed For the relief of dyspnea, oxygen inhalations are given Otherwise, therapeutic measures are instituted according to general and pulmonary findings When pulmonary changes result from long continued industrial exposure, the patient should be protected from irritating fumes and given symptomatic treatment Acute and purulent expectoration calls for the administration of penicillin by inhalation or intramuscularly, provided micro-organisms sensitive to this antibiotic are found in the sputum Bronchiectasis is treated according to the outline given in the respective chapter

Nickel Carbonyl ($Ni(CO)_4$) *is a gaseous liquid* Its fumes are harmful to the mucosa of the respiratory tract Dangerous concentrations vary from 0 05 to 0 5 per cent Exposure occurs in connection with the production of pure nickel The interval between exposure and the development of symptoms is from 12 to 24 hours The patient is found to have cough with blood tinged sputum, dyspnea, cyanosis and occasionally delirium The treatment is based on the lung findings and follows the pattern outlined for the management of patients with pulmonary dam

age due to noxious gases Prevention can be efficiently carried out by providing employees with supplied air respirators.

High incidence of primary bronchogenic carcinoma has been recorded among workers employed in nickel ore refineries

Nitrous Fumes are reddish brown in color and have a pungent odor They contain the poisonous oxides of nitrogen, namely nitrogen monoxide (nitric oxide) (NO), nitrogen dioxide (NO_2) and nitrogen peroxide (N_2O_4) Their inhalation in large quantities is followed either by asphyxia or by more or less severe damage to the lung In concentration of 60 parts per million, they inhibit the normal ciliary function of the respiratory mucous membrance according to the experimental studies of Cralley Pathologic changes in the lung are caused by the formation of nitric acid from the chemical union of NO_2 and H_2O of the bronchial mucous membrane

Clinically, one finds a variety of pulmonary changes after exposure to nitrous fumes These are bronchitis, bronchial ulceration, miliary or patchy bronchopneumonia, lobar pneumonia or pulmonary edema The latter is attributed to the increased capillary permeability about the alveoli, brought about by the local effect of nitric acid Pneumonic infiltrations are due to the chemical action of nitric acid as well as to pathogenic microorganisms which readily settle down in areas damaged by the acid

Exposure to these fumes over a prolonged period of time is likely to be followed by chronic bronchitis pulmonary fibrosis, with dyspnea and asthmatic wheeze and emphysema Jones and Lockhard noted that persons with arrested tuberculosis who work around concentrated nitrous fumes had a tendency to rapid appearance of pulmonary hemorrhage

Tollman and his associates were able to reproduce pathologic changes in animals exposed to nitrous fumes In cases of immediate asphyxial death, there was no gross evidence of pulmonary edema or bronchial occlusion The blood vessels were filled with chocolate brown blood characteristic of the presence of methemoglobin The latter was confirmed by spectral analysis Methemoglobin forms from the chemical interaction of the nitrite ion and hemoglobin As in the case of carbon monoxide poisoning asphyxiation results when 80 per cent of the hemoglobin is replaced by methemoglobin and consequently, the body tissues are deprived of their normal oxygen supply Examination of the lungs of animals which died of pulmonary edema revealed depressed patchy water logged areas alternating with similarly distributed somewhat ele-

vated *emphysematous areas* The bronchi and larger bronchioles contained edema fluid Necrosis and desquamation of the lining cells were noted in the smaller bronchi which were filled with exudate composed of epithelial cells mononuclear leucocytes and edema fluid Similar changes were observed *in the alveoli the atriums and alveolar ducts* Capillaries of the alveoli, for the most part, were dilated and congested When pneumonia was the cause of death *of the experimental animals* death occurred from several days to several weeks after the exposure to oxides of nitrogen Examination of the lung showed extensive fibrinous pleural adhesions and many areas of patchy consolidation Microscopic inspection of the latter revealed a heavy cellular infiltration and exudation in the alveoli, alveolar walls, atriums, alveolar ducts, bronchioles and bronchi Also there were congestion and thickening of the alveolar walls throughout the lung Large abscesses and gangrene were frequently seen Compensatory emphysema was observed in the noninvolved areas of the lung

Exposure to oxides of nitrogen occurs in the chemical and hat industries, dyeing, electroplating engraving photogravure processes, metal cleaning, oxyacetylene welding electric arc welding and carbon arc welding Welding represents a definite industrial hazard when it is done in small, confined places Also, oxides of nitrogen may originate from incompletely detonated nitro explosives

Sometimes there is an incubation period of several hours before symptoms become manifest These include cough tightness in the chest dyspnea, cyanosis and expectoration of frothy, blood tinged or yellow *sputum* The yellow color of the latter is due to a chemical combination *of proteins with nitric acid* Tightness *in the chest* is attributed to extensive alveolar *and bronchiolar* occlusion by the edema fluid and also to reflex bronchospasm Cyanosis and dyspnea are brought about by two factors

1 Anoxia caused by the loss of respiratory surface area on account of pulmonary edema

2 The formation of methemoglobin in the blood which obviates the transportation of normal amounts of oxygen by *the red blood cells* Patients who develop pneumonia complain also of persistent severe chest pain This is due to the associated extensive plastic pleurisy Fever is a common occurrence in these cases

The location extent and intensity of physical and roentgenologic findings depend upon the type and severity of the pulmonary pathologic

changes A detailed discussion of such findings is presented in the chapters on *Bronchitis Pulmonary Edema and Pneumonia*

The mortality rate is high in persons following inhalation of oxides of nitrogen in concentrations stronger than 1 10 000 even when the exposure lasts for a few minutes only A sad example of this is the Cleveland Clinic disaster caused by NO poisoning from x ray film fire The only exception is nitrous oxide (N_2O) which is used as an anesthetic gas

Death may ensue within five minutes of the inhalation of the other oxides of nitrogen Also, the prognosis is grave when pneumonia develops unless early treatment is instituted with adequate supportive measures and with the administration of antibiotics so as to combat secondary bacterial invasion which is common in these cases

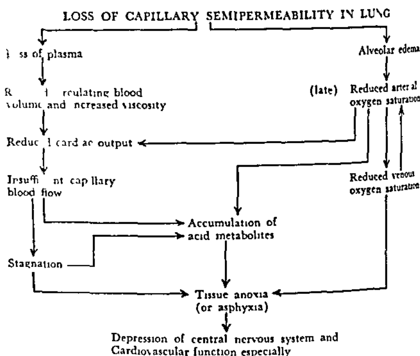
Paraphenylened amine ($C_6H_4[NH_2]_2$) is used in the fur and rubber industries and photographic work When it is inhaled in the form of vapor or dust it may cause asthma like syndrome and bronchitis with severe mucosal edema Prevention of exposure is as important as with other noxious gases fumes and dusts Satisfactory symptomatic relief can be obtained in the treatment of respiratory manifestations from the administration of broncho dilator drugs such as theophyllin with ethylenediamine (aminophyllin) given either intravenously or intramuscularly and from the periodic inhalations of 0 5 or 1 0 cc of aerosolized 1 100 solution of epinephrine or neosynephrin

Phosgene (carbonyl chloride) ($COCl_2$) is a colorless gas which has the smell of fresh cut hay and is about three and a half times heavier than air It is the most effective lung irritant used in chemical warfare In outdoor air its damaging action may become manifest in less than half an hour after exposure The salient pathologic changes are inflammation and edema of the bronchial and bronchiolar mucosa and alveolar edema Durlacher and Bunting demonstrated the occurrence of consolidation of one or more lobes of the lung in dogs from four to nine days after exposure to phosgene, 0 29 mg per liter for 30 minutes Also they observed pulmonary organization after the subsidence of initial edema

The patient complains of cough, thoracic pain tightness in the chest wheezing and dyspnea These symptoms are likely to be associated with cyanosis The patient may appear gray due to shock

Physical and roentgenological findings are characteristic of pulmonary edema or consolidation Evidence of right ventricular strain may be noted Laboratory findings are those usually found in pulmonary

edema, namely decreased velocity of blood flow, increased viscosity of the blood, together with increased hemoconcentration, increase in hemoglobin and a high erythrocyte count which may reach 9,000,000 per cubic millimeter The probable sequence of abnormal physiologic changes in phosgene poisoning is well illustrated in the diagram published by Bruner and his associates



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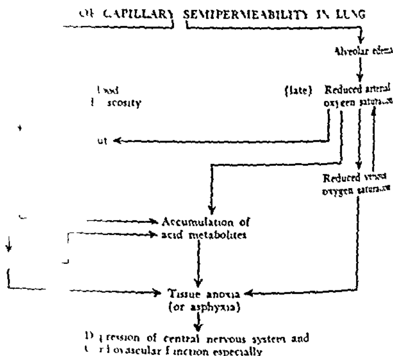
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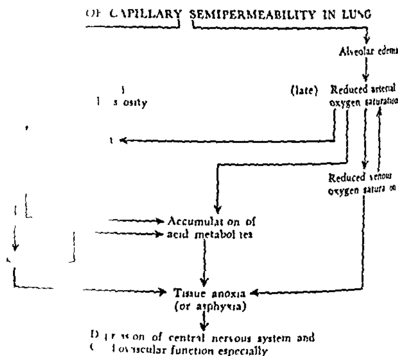
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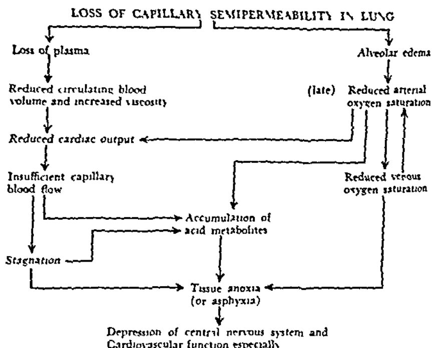
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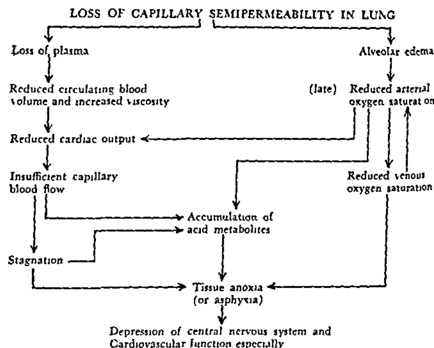
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initial pulmonary irritation caused by exposure to low concentrations of hydrogen selenide was followed by an acute diffuse pneumonitis which in some cases was associated with bronchopneumonia A case of pure hydrogen selenide poisoning in a chemist was recorded by Senf While working in a laboratory, the patient first noticed a garlic odor, then developed lacrimation, coryza hoarseness and dyspnea There was a purple rash on both cheeks Numerous moist rales were audible over the lungs the respiratory excursions of which were limited The facial rash disappeared in ten days The edema of the lung, dyspnea and cyanosis subsided slowly There were no red selenium traces in the urine

Acute manifestations of industrial selenium poisoning were reported by Clinton, in connection with smelting of plates from selenium rectifiers for scrap He recommends discarding old rectifier plates on account of this hazard Symptoms of acute selenium poisoning are cough and other manifestations of pulmonary edema, together with abdominal colic, and diarrhea Also one finds frontal headache, dizziness, lacrimation and sneezing In the chronic form, there are symptoms and signs of nasopharyngeal and bronchial irritation, persistent garlic odor on the breath and gastrointestinal disturbances Roentgenograms of the chest reveal findings typical of pulmonary edema In chronic cases there are no abnormal roentgenologic changes

Following very brief exposure, the prognosis of acute selenium poisoning is good Symptoms and physical findings may clear in twenty four hours Appropriate management of these cases consists of adequate treatment of the pulmonary edema and bronchitis, as outlined in the respective chapters

Shellac Shellac a purified lac, is a pale yellow natural resin of insect origin, which contains a mixture of fatty acids The material from which the purified product is obtained is known as stick lac It is found in the form of incrustation on twigs of plants which serve as hosts for the insect coccus lacca Dissolved in alcohols amyl acetate, turpentine or linseed oil, shellac is used as the main ingredient of lacquers and varnishes When minute droplets of shellac are inhaled during its use as a spray in various industries, pathologic changes take place in the lung which are similar to those caused by known irritating oils

Hirsch reported a case of a man engaged in the manufacture of furniture who was exposed to varnishes for many years The patient's complaints were chronic, nonproductive cough fatigue and weakness of several years' duration and gradually increasing dyspnea for nine

months Physical examination revealed inspiratory rales Roentgenograms of the lung showed extensive infiltration, especially of the right lung Interference with respiratory function as the cause of progressive, severe dyspnea was recognized from the analysis of gases of the blood On postmortem examination, the following pertinent findings were noted Macroscopically, there were pronounced chronic indurative pneumonia of both lungs, fibrinous pleurisy on the right side and fibrous pleurisy on the left side There was evidence of diffuse and nodular consolidation of gray and grayish red color

Subsequent experimental studies carried out by Hirsch substantiate the assumption that the inhalation of shellac is capable of causing exudative and indurative pneumonias Nodular areas of consolidation, with foci of necrosis were produced in rabbits by intratracheal instillation of an emulsion of commercial shellac during an observation period of 44 days Identical but even more pronounced pathologic changes were observed by *the same investigator when a lac like material extracted* from this patient s lung was used for intratracheal instillation in rabbits

Sulphur Dioxide (SO_2) is a pungent gas Exposure to it occurs at its production and its use in bleaching processes, preservatives, refrigerators and in the manufacture of gelatine and glue from bones and various other chemical processes Also, pulmonary damage due to sulphur dioxide may occur from the inhalation of the exhaust gases of Diesel engines and in founding magnesium alloys

Sulphur dioxide is capable of causing severe bronchitis, bronchopneumoia, lobar pneumonia or pulmonary edema, with corresponding symptoms and objective findings Cralley observed that concentrations of sulphur dioxide of 30 parts per million and over, lead to cessation of the ciliary function of the mucous membrane of the air passages

The development of pulmonary edema entails serious prognosis Fatal termination may occur as early as in 24 hours Patients who recover from pulmonary affections caused by sulphur dioxide are likely to develop bronchiectasis, bronchial asthma or respiratory insufficiency The severity of pneumonia is attributed partly to invasion by secondary pathogenic microorganisms For this reason it is necessary to use penicillin or streptomycin in the treatment of this condition For details of treatment, the reader is referred to the respective chapters

Tetraethyl Orthosilicate (Ethyl silicate) ($[C_2H_5]_4SiO_4$) is an organic silicon compound with water like color and a distinct sharp ordor It is used as a vehicle for inorganic pigments as a source of pure silica gel,

as a waterproofing agent for stone and concrete and as a bond in ceramic materials Kasper and his associates conducted experimental studies on its toxicity They found that the major initial pathologic changes develop in the lung following the inhalation of this compound These were pulmonary hemorrhages and secondary pneumonia In addition they noted the occurrence of anemia acute nephritis and hematuria The subsequent experimental work of Smyth and Seaton confirmed these findings, with the qualification that pathologic changes in the lung were observed in only 22 per cent of the animals They state that 500 parts per million is the maximum exposure for several hours without causing serious disturbance

Tetryl [$(NO_2)_3 C_6H_2N(CH_3) NO_2$], chemically known as tetranitro methylaniline, is one of the nitro explosives It is a yellow crystalline powder Massive exposure to its dust during processing may lead to cough, dyspnea and asthma like attacks The latter are especially severe at night Other possible manifestations of tetryl intoxication include nervousness, headache, irritability, insomnia, malaise frequent epistaxis sneezing nausea abdominal cramps loss of weight irregular menstruation and dermatitis Yellow discoloration of the skin is a common finding Because of this condition these individuals are alluded to in their communities as "canaries" According to Witkowski and his associates 23 per cent of people engaged in processing this compound develop symptoms of tetryl illness Roentgenologically demonstrable pathologic changes in the lung may be entirely absent In some instances, fibrosis and emphysema are found as reported by Hardy and Maloof It is likely that the asthmatoid attacks are due to bronchospasm possibly attributable to sensitization

Trichlorethylene ($CHClCCl_2$) is a liquid with chloroform like odor It is a widely used detergent and industrial solvent Also, it has an extensive application in the removal of oil and grease from metal parts Inhalation of its vapors is bound to cause a state of intoxication similar to alcoholic intoxication which is followed by coma Moderate exposure to it induces congestion of the mucous membrane of the respiratory tract Massive inhalation of its vapors is likely to lead to severe pulmonary edema

Trichloroacetonitrile (CCl_3CN) is a fumigant and insecticide The experimental studies of Treen and his colleagues showed that prolonged inhalation of its vapors in concentrations higher than 1 0 mg per liter caused severe acute tracheobronchitis alveolar edema interstitial and

parenchymal pneumonia, massive hemorrhagic extravasations and degenerative changes in the pulmonary vessels

Turpentine oil is used in the chemical and pharmaceutical industries, particularly in the production of synthetic camphor and in the manufacture of lacquers, shoe creams and polishing waxes Turpentine is an excellent solvent for oils, fats and resins Inhalation of large amounts of its vapors is likely to cause bronchitis and rarely, pneumonia Following the removal of the patient from the source of exposure, adequate measures are available for the treatment of these conditions

Vanadium anhydride was found by Molfino to have a severe irritating action upon the respiratory tract, including the lung

Wood dust as a possible causative agent of respiratory diseases was investigated experimentally by Bergman and his associates (1943) Animals exposed to wood dust developed pulmonary changes which varied from bronchopneumonia to large abscesses On the basis of their observations, these workers arrived at the conclusion that wood dust in concentration of 10,000,000 particles per cubic foot of air, breathed for periods of eight hours a day, five and a half days a week, in rabbits is harmful, causing irritation of the air passages, which predisposes to bronchitis, pneumonia and tuberculosis Also, they expressed the view that similar long exposure may be injurious to some if not all human beings

Zinc chloride Concentrated zinc chloride ($ZnCl_2$) smoke is injurious to the mucous membrane of the respiratory tract Its inhalation causes acute laryngotracheobronchitis

In closing, we wish again to emphasize the utmost importance of preventive measures These include adequate ventilation of the work place, competent exhaust equipment at the site of origin of noxious fumes, dusts and gases, the wearing of respirators which contain satisfactory filters and gas absorbent cartridges, wearing of protective hoods or helmets with positive pressure air intake In addition, general health education and efforts toward promoting and maintaining normal physical vigor are useful adjuncts

The following code prepared by Bowditch and his associates (1940) has been in use in Massachusetts for some time and can serve as a valuable guide in industrial hygiene

Code for Safe Concentrations of Certain Common
Toxic Substances Used in Industry

Maximum Concentrations

Gas or Vapor	*Parts per Million*
Ammonia	100
Amyl acetate	400
Aniline	5
Arsine	1
Benzene	75
Butyl acetate	400
Cadmium	0 1*
Carbon bisulfide	15
Carbon monoxide	100
Carbon tetrachloride	100
Chlorine	1
Chlorodiphenyls	1*
Chloronaphthalene	1-5*
Chromic acid	0 1*
Dichlorbenzene	75
Dichlorethyl ether	15
Ether	400
Ethylene dichloride	100
Formaldehyde	20
Gasoline	1000
Hydrochloric acid	10
Hydrogen cyanide	20
Hydrogen fluoride	3
Hydrogen sulfide	20
Lead	0 15*
Mercury	0 1*
Methyl alcohol	200
Monochlorbenzene	75
Nitrobenzene	5
Nitrogen oxides	10
Ozone	1
Phosgene	1
Phosphene	2
Sulphur dioxide	10
Tetrachlorethane	10

Tetrachlorethylene	200
Toluene	200
Trichlorethylene	200
Turpentine	200
Xylene, coal tar naphtha	200
Zinc oxide fume	15*

*Milligrams per cu meter

Treatment When the patient is first seen after massive inhalation of one of the toxic gases or fumes, immediate attention should be focused on the management of shock and on the control of the pulmonary condition Unproductive cough is a useless and harmful cough It either should be changed so that it becomes productive or it should be suppressed For the latter purpose, it is expedient to prescribe codeine in doses of ½ to 1 grain (0 03 to 0 06 Gm) or dicodid in doses of 1/12 to 1/6 gr (5 to 10 mg) three times a day Dicodid is the bitartrate salt of dihydrocodeinone It is a ketone type of morphine derivative

Inhalation of a mixture of 5 per cent carbon dioxide and 95 per cent oxygen acts as a most efficient expectorant It is capable of liquifying tenacious, sticky, viscous exudate into a watery kind In this manner, expectoration of inflammatory products from the bronchi is greatly facilitated Its administration renders the use of potassium iodide and other expectorants superfluous The inhalations are given through a face mask and with a gas flow of 5 liters per minute every hour or every two to three hours for several days if necessary The frequency of inhalations is decreased with improvement in the pulmonary condition

In addition to being an excellent expectorant, carbon dioxide is of value on account of its stimulating effect upon the respiratory center Inhalation of carbon dioxide in medicinal doses is followed by deep inspirations and vigorous expirations The enhanced respiratory motions of the lung are instrumental in ventilating off noxious gases

Moreover, with the augmented respiratory movements of the lung, there is a simultaneous improvement in the competency of the pulmonary blood circulation This in turn is bound to remove transudated plasma from the alveoli and thus, alleviate pulmonary edema The therapeutic use of carbon dioxide is contra indicated when acute plastic pleurisy or pronounced hypertension is present

Barach recommends the inhalation of a mixture of 75 per cent helium and 25 per cent oxygen in cases with widespread bronchial and bronchio

lar occlusion This gas mixture is three times lighter than atmospheric air therefore, it penetrates to the alveoli through *narrowed air passages* more readily and with less respiratory effort than air does

Most persons exposed to the *massive inhalation of noxious gases and* fumes develop some degree of bronchospasm This is likely to cause added *anoxia and dyspnea Also, it interferes with the* expectoration of edema fluid and thus it aggravates the patient s distress Bronchospasm *is best counteracted by theophylline* with ethylenediamine (aminophyllin) It is given in doses of 7½ grains (0 5 Gm) in 20 cc of water intra venously twice or three times a day It is mandatory to give these intra venous injections slowly, not more than 2 cc per minute by the watch so as to avoid disturbing general reactions and syncope Theophylline with ethylenediamine can be administered rectally in the form of sup positories or by instillation Commercially available suppositories con tain 7½ grains (0 5 Gm) of the drug The same amount can be dis solved in tap water and given through a No 12 F catheter

The inhalation of aerosolized neosynephrin and epinephrine was recommended by Segal and Aisner A mixture of 1 cc of 1 per cent neosynephrin and 0 5 cc of 1 100 epinephrine is inhaled with the aid of a nebulizer four or five times a day The nebulizer is connected to an oxygen tank with a controlled gas flow of 5 to 6 liters per minute The discharge tube of the nebulizer is held in the mouth A single treat ment takes about 20 minutes The benefits of this measure are attributed to the influence of neosynephrine as an effective vasoconstrictor and of epinephrine as a good bronchodilator

Kennedy and his associates reported treatment of two patients with beryllium granulomatosis and one with silicosis with ACTH 100 mg daily for varying periods Improvement was observed, with an evident feeling of well being and strength but the symptoms recurred when the therapy was discontinued

Mention should be made of certain therapeutic ' don ts ' According to the experimental observations of Bruner and his associates no ther apeutic benefits can be expected in pulmonary edema from the adminis tration of concentrated plasma, pectin solution gelatine solution pos terior pituitary solution and isotonic solution of sodium chloride.

Without definite proof of heart failure, *these patients should not be* given digitalis Neither is any constructive purpose served by caffeine or strychnine in these cases

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CHAPTER XVII

CONGENITAL DISEASES OF THE LUNG

AGENESIS (APLASIA) OF THE LUNG

By Andrew L Banyai, M D and J Winthrop Peabody, M D

Congenital absence of the lung is a very rare condition Olcott and Dooley (1943) found only one case recorded out of 10,000 necropsies made on newborn infants Up to 1952, less than 100 cases have been reported in the medical literature, most of them in infants and children Some of these individuals, however, lived to 58, 65 and 72 years of age and died of causes unrelated to their pulmonary condition

Three types of pulmonary agenesis (aplasia) have been described by *Schneider (1913)*

1 One lung is entirely absent, together with the corresponding blood vessels and main bronchus

2 The missing lung is represented by a small out pocketing of the trachea, which corresponds to a primordial bronchial bud

3 There is a very small bronchus on the affected side, which ends in a blind pouch and connects to a tiny mass of rudimentary lung tissues The latter shows the characteristics of a fetal lung, with atelectasis, few alveoli and bands of connective tissue This condition should be referred to as hypogenesis of the lung

Interestingly, agenesis of the lung has been found more often in the male than in the female The left lung was absent twice as often as the right lung Various theories have been advanced as to the pathogenesis of this condition The only pertinent tenable concept was proposed by Schwalbe (1913), who attributed it to an endogenous predisposition which originated from a faulty germ plasm In favor of this theory speaks the presence of other manifestations of general maldevelopment These include unilateral hypoplasia of the face corresponding to the affected side, dermoid of the eye, malformation of the external ear, anomalous vertebrae, wedge shaped hemivertebrae, spina bifida, synostosis of ribs, absent wrist and hand, absence of one radius, cleft palate,

bifid uvula, harelip, esophageal stenosis or atresia, esophago-tracheal fistula, absence of the diaphragm on the affected side, with consequent eventration of the small intestine and part of the colon into the hemithorax on the same side, Meckel's diverticulum, agenesis of liver and spleen, absence of one kidney, ureter, ovary and Fallopian tube, hypoplasia of liver and spleen, accessory spleen, anomalous renal vessels, atrophy of suprarenal glands, accessory or hypertrophied thymus, absent vagus, exencephaly and various anomalies of the heart and large vessels, such as ventricular septal defect, patent foramen ovale, patent ductus arteriosus, hydropericardium, pericardial adhesions and absence of the division of the truncus arteriosus of the aorta

The affected hemithorax is occupied by the heart and is filled by a displacement of the other mediastinal structures, some adipose tissue, sometimes by watery fluid, persistent thymus, and by expansion of the functioning lung from the opposite side Pulmonary vessels are absent from the affected side The main bronchus may be represented by a thin, rudimentary structure, from 1 to 3 cm in length or just by a small cul de-sac of the trachea The lung of the unaffected side shows various deviations from normal Usually, it is increased in size and may show no divisions into lobes, the interlobar septums may be imperfectly formed Rudimentary lower lobe and supernumerary lobes have also been described Instead of one main bronchus, two or three bronchi may branch from the trachea to the lung There is only one pulmonary artery and one pulmonary vein The latter may enter the azygos vein instead of the left auricle

Symptoms

Symptoms are predicated upon the respiratory competency of the lung and on the presence of other anomalies which have direct bearing on the viability of the patient Approximately 14 per cent of those reported were stillborn or died within the first week of life Others have been known to go through life without restriction of physical activities or even being conscious of respiratory embarrassment Between these two extremes, cases have been observed with dyspnea, cyanosis, stridor, stertorous breathing, harsh inspiratory crow, recurrent choking spells, periodically recurring cough, expectoration, pulmonary hemorrhage and failure to thrive in younger patients

Diagnosis

Physical examination may reveal asymmetrical chest or a decrease in the size of the affected hemithorax Scoliosis, with its convexity toward or away from the affected side, may be noted The respiratory expansions of the chest are usually lagging on one side and are exaggerated on the other side The percussion note is dull or flat and the breath sounds are absent corresponding to the absence of the lung In case of a marked tracheal shift, bronchial breathing may be audible When the uninvolved lung expands well over the affected side, breath sounds are heard along the sternal border The heart is always displaced toward the affected side

Roentgenologic examination of the chest shows characteristic findings The affected hemithorax is smaller than the opposite side and casts a homogeneous, dense shadow In contrast, the good lung reveals increased translucency and a tendency to extend toward the affected hemithorax Also, one can visualize a displacement of the heart and mediastinal structures in the same direction Barium is used for determining the exact position of the esophagus and possible esophageal stenosis In addition the roentgenogram of the chest shows an elevation of the hemidiaphragm and a narrowing of the intercostal spaces on the involved side

Instillation of iodized oil is most valuable in clarifying the diagnosis Technical details of this procedure are given in the Chapter on Bronchiectasis By this means, one can ascertain the size, shape and position of the trachea and bronchi The trachea may be normal in size or somewhat elongated, with a shift toward the affected side The oil instilled reveals the complete absence of the main bronchus on one side or in its stead one will note a bud like sac filled with oil, representing the rudimentary main bronchus In other cases, a short narrow main bronchus may be visualized which leaves the trachea at an acute angle

Bronchoscopic examination is indispensable for correct diagnosis and differential diagnosis In some of the cases reported, technical difficulties arising from the anomalous anatomical changes obviated satisfactory bronchoscopy When, however, free visualization of the lower respiratory tract is possible, the examination reveals a trachea of even, uniform width, its direct continuation into one main bronchus, the absence of the carina and the other main bronchus In some cases, a rudimentary bronchial branch or tracheal diverticulum was noted, corresponding to the missing main bronchus. Also, bronchoscopy may show

two or three bronchi branching from the trachea to the good lung instead of one main bronchus

The symptoms, physical and some of the roentgenologic findings may be suggestive of conditions other than agenesis of one lung From the differential diagnostic standpoint, one should consider fetal and acquired massive atelectasis, (in children particular attention should be paid to possible foreign body aspiration), diaphragmatic hernia, paralysis of the hemidiaphragm, pneumonia, pleural effusion, pleural thickening, massive fibrosis and postpneumonetomy status

With the aid of the aforementioned diagnostic methods, the exact diagnosis should be established without difficulty

Prognosis

The prognosis is greatly influenced by coexistent developmental anomalies which may handicap the patient's life expectancy Also, the relatively high incidence of pneumonia must be kept in mind

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CONGENITAL ALVEOLAR DYSPLASIA OF THE LUNGS

By Andrew L Banyai, M D and J Winthrop Peabody, M D

Mac Mahon in 1947 first called attention to a congenital developmental anomaly of unknown etiology, which he designated as congenital alveolar dysplasia of the lungs This condition is encountered in premature infants and also, in children born at term Examination of the pathologic specimen shows that the lung is as large or larger than normal and of fleshy consistency The cut surface is dark red Mac Mahon observed the following characteristic histologic findings "There are too few alveoli and too much interstitial tissue In its extreme form the lung seems to be composed of an excess of embryonal but highly vascularized mesenchymal tissue containing numerous well formed bronchi and bronchioles that lead into branching alveolar ducts In other cases in which the changes are less severe, the histologic picture superficially resembles an immature lung of about the fourth or fifth months of gestation"

According to Mac Mahon, children with congenital alveolar dysplasia of the lungs may live from a few hours to a few weeks Progressive dyspnea and cyanosis dominate the clinical picture The patient's condition may be aggravated by atelectasis pulmonary congestion, edema, hemorrhage, bronchiolitis and pneumonia Physical and x-ray findings are suggestive of atelectasis

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CONGENITAL TRACHEOESOPHAGEAL FISTULA

By Andrew L Banyai, M D and J Winthrop Peabody, M D

Congenital tracheoesophageal fistula without associated atresia of the esophagus is extremely rare Its symptoms are the same as those encountered in patients with acquired tracheoesophageal fistulas, namely coughing spells on swallowing nourishment, particularly liquids Respiratory distress and cyanosis are noticeable during coughing paroxysms Regurgitation of food is bound to provoke the same symptoms The resulting interference with normal nutrition leads to dehydration and malnutrition When the fistula is very small, cough coincident with feedings is slight and months or years may go by before medical attention is sought

Haight emphasizes the importance of roentgenologic examination with the aid of iodized oil instilled into the esophagus while the patient is in the prone position In this manner one can readily note the entrance of the iodized oil from the esophagus to the trachea Tracheosocopy and esophagoscopy are likely to detect the presence of tracheoesophageal fistula A swallow *of a solution of methylene blue or gentian violet prior* to tracheoscopy facilitates the demonstration of the fistulous tract Since the report of Lamb it is known that large amounts of air may accumulate in the stomach and intestines of patients with tracheoesophageal fistula Physical and x ray examinations of the chest may reveal secondary pathologic changes in the lung These and pertinent differential diagnostic pointers are described in the chapter on Bronchial Fistulas

The treatment is surgical Imperatori (1939) and Haight (1948) reported successful correction of congenital tracheoesophageal fistula

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CYSTIC DISEASES OF THE LUNGS

By FRANCIS M WOODS, M D and RICHARD H OVERHOLT, M D

Cystic diseases of the lung are in reality a group of diseases of varied origin In this category are included all the various abnormal fluid or air containing spaces that are not directly dependent upon lung destruction In practice it is often impossible to distinguish clinically and even pathologically abnormal cystic spaces from inflammatory or other destructive processes

Historical Notes

The vast development both of roentgenology and of thoracic surgery of the past 25 years has stimulated increase in knowledge of pulmonary cystic diseases What was considered a rare abnormality is now recognized as common The report of Thomas Bartholinus in the Leyden edition of Malpighius in 1687 is recognized as the first in medical literature He recorded two cases in children and one in an adult in which a lung was replaced by a "membranous vesicle" filled with air or pus By 1925 Koontz, who wrote the first American paper, had found 108 case reports in European literature He described the case of a child in whom at autopsy numerous congenital cysts were found in both lungs Since then several hundred cases have been recorded As is often the case in new fields of knowledge, understanding of pulmonary cysts has been retarded by diverse explanations of origin and confusing systems of nomenclature More recently clarification has begun to emerge, thanks in part to such useful classifications of cysts as those proposed by Maier and Clagett The foundations of surgical therapy were laid by Sauerbruch, Clairmont, and Eloesser and other pioneers Clairmont attempted lobectomy for cystic disease of an entire lobe but the patient, a boy of 10, died Sauerbruch in 1927 reported four successful extirpations or lobectomies He had recognized the true nature of the condition in the first two when he drained what was thought to be an empyema Noting that the infection was within the lung tissue, he realized that he was dealing with a secondarily infected lung cyst and later performed resection In the last two, the true condition was recognized and resection was the primary treatment Eloesser reported a similar experience in 1928 when he drained and later resected a left lower lobe His patient also had a left upper lobe cyst not producing symptoms

Classification

Clagett's classification of lung cysts is useful and practical He divides them into those of bronchial origin and those of alveolar origin Maier had included other categories which do not clearly belong under this heading, but will be mentioned here because in actual practice no sharp line can be drawn between the various groups

A Bronchogenic Cysts

B Cysts of Alveolar Origin

1 Pulmonary blebs

2 Bullae

3 Pneumatoceles

C Cystic Bronchiectasis

D Acquired intrapulmonary cavities originating in lung destruction

A BRONCHOGENIC CYSTS

In general, it may be stated that the majority of bronchogenic cysts are congenital in origin while the various cysts of alveolar origin are due to postnatal developments Most bronchogenic cysts have an epithelial lining consisting of cuboidal, columnar, or pseudo stratified epithelium, but the epithelium may have been destroyed by infection They may be single or multiple but single cysts are usually bronchogenic The wall may be smooth or trabeculated Usually there are one or more communications between these cysts and the bronchial system, and it is through these openings that infection gains access to the cysts At times infection or the resulting fibrosis in or about the communicating bronchi may allow ingress of air more easily than egress and this check valve mechanism leads to distention of the cyst with air However, this is less common than in the cysts of alveolar origin Symptomatology depends upon the size and location of the cysts, and the presence or absence of infection Many produce no impairment of pulmonary function, and are found only at autopsy or by routine chest x ray Others displace or compress sufficient lung tissue to produce dyspnea and cyanosis The degree of difficulty will obviously depend upon the amount of lung tissue compressed and the rapidity of onset will parallel the speed of enlargement of the cyst If the cyst or cysts do not communicate freely with the bronchus, they may fill with secretions and gradually enlarge and thus decrease lung function The local irritating effects on bronchi may produce cough and expectoration and, occasionally, blood spitting When secondary infection develops, the cyst becomes a special type

of lung abscess, there will be fever, cough, and expectoration often of foul material The infection is likely to be low grade with comparatively little absorption of toxic materials through the epithelial cyst lining Recurrent bouts of infection heralded by vague chest pain are frequent

B CYSTS OF ALVEOLAR ORIGIN

Cysts of alveolar origin are rarely single They may be widespread or localized to one lobe or one segment of a lobe All conceivable distributions are seen Their origin is found in emphysema or inflammatory processes producing obstruction to terminal bronchioles and dilatation of alveoli

When alveoli rupture and allow air to dissect between the parenchyma and the visceral pleura a pulmonary bleb is formed The outer wall of such a sac glides over the underlying parenchyma Such blebs are usually found in emphysematous lungs Occasionally a group or rarely a single such sac will become sufficiently distended to produce dyspnea Secondary infection is uncommon due to the minute bronchiolar communications Most do not produce symptoms However, they do rupture, allowing air to escape into the pleura A tension pneumothorax develops with associated chest pain and dyspnea Tension or spontaneous pneumothorax may be secondary to tuberculosis in some instances but it is now believed that the vast majority are caused by ruptured pulmonary blebs without any underlying infectious process

It is impossible to consider emphysematous bullae and pneumatoceles separately Bullae are defined as non epithelialized pulmonary cavities produced by the rupture of interalveolar septa Presumably, their origin is due to mechanical overstretching of alveoli Pneumatoceles have been defined as non epithelialized positive pressure cavities produced by hyperinflation of a defect in the parenchyma resulting from infection Such spaces may be transient following acute pulmonary infections in children or even adults Coffey believed them to be due to a check valve mechanism in bronchioles secondary to a localized obstructive inflammatory process Practically the etiology of the two is only distinguished with difficulty by the pathologist and rarely by the clinician The treatment is the same The vital point of distinction between bullae and pneumatoceles on the one hand, and blebs on the other is that the latter are located on the lung surface, the former, are within the parenchyma These cysts deep within the lung rarely rupture to form a tension pneumothorax Many do not produce symptoms

Those that do give dyspnea increasing as the cysts become larger Often the cysts are in clusters Secondary infection is less frequent than in bronchogenic cysts

C *Cystic Bronchiectasis*

Terminal portions of bronchi are commonly dilated into sac formations in bronchiectasis Occasionally one or more such sacs are markedly dilated and difficult to distinguish from other forms of pulmonary cysts especially those with bronchial communications Clusters of thin walled pulmonary cysts associated with nearby dilated bronchi are occasionally observed Whether the cysts or the dilated bronchi are the primary trouble it is impossible to say In brief all gradation ranging from pure bronchiectasis to pure cysts occur Bronchiectatic cavities do not strictly belong in a discussion of cystic disease of the lungs but cannot be clearly separated

D Acquired Intrapulmonary Cavities Originating in Lung Destruction

Acquired intrapulmonary cavities originating in lung destruction are cystic spaces actually constituting the end result of lung abscesses Usually there is no difficulty in distinguishing pulmonary cysts from cystic spaces resulting from lung abscesses At times such spaces fail to heal because bronchial mucosa grows in over the lining surfaces from communicating bronchi At other times a check valve mechanism in the communicating bronchus prevents collapse of the abscess One must presuppose a relatively low grade infection with or without a check valve mechanism in the draining bronchi It may be impossible to distinguish clinically or even pathologically between a bronchial cyst with secondary infection and a chronic abscess with an acquired epithelial lining Thus the acquired pulmonary cavity originating in lung destruction although not strictly one of the cystic diseases of the lung must be considered as such Rarely a cyst will be found which is secondary to carcinoma tuberculous stenosis or other process blocking a bronchus

Mechanics of Lung Cavities

No sharp line can be drawn between lung cysts of various origins—bronchial alveolar bronchiectatic or destructive However understanding of the mechanism of production and maintenance of such spaces is important As Maier has pointed out the production of a cavity presupposes

(1) A congenital defect

(2) Destruction of pulmonary tissue by inflammatory or other process

(3) Hyperinflation of a defect in pulmonary parenchyma

(4) A combination of the above factors

Persistence of such a cavity presupposes one or more of the following

(1) Positive pressure within the cavity

(2) Progressive destructive processes within the cavity

(3) Loss of expansibility of surrounding tissue

(4) Loss of elastic properties of the cavity wall

(5) Epithelialization of the cavity wall

Symptomatology

The symptomatology of lung cysts is best understood in relationship to mechanical factors which may apply to any one of the types of cysts They may be grouped as follows

(a) Symptoms due to enlargement of cysts and displacement of the remaining lung tissue (largely caused by bullae and pneumatoceles)

(b) Symptoms due to perforation of cysts into the pleura (largely emphysematous blebs)

(c) Symptoms due to infection within cysts (largely bronchogenic cysts)

It must be emphasized that any one of the types of cysts may produce any of the above groups of symptoms, but that each type due to its location or mechanical factors is most likely to produce a particular type of symptom It is also true that many cysts produce no symptoms

(a) As single or multiple cysts gradually enlarge neighboring lung tissue is displaced and compressed cutting down on pulmonary reserve This gives rise to dyspnea which may be mild, or in advanced cases, severe In extreme cases respiration may be labored and accessory muscles of respiration may be called into play There may be cyanosis, clubbing of fingers, and even death due to respiratory failure Extreme symptoms may be precipitated by secondary bronchitis or pneumonitis Usually they develop gradually and progressively in adults In infants, however, they may appear and disappear rapidly Coffey described this process in infants during the course of lobar pneumonia

(b) The symptoms of spontaneous pneumothorax are well known sudden chest pain and rapidly developing dyspnea and occasionally



Fig 2A

Case 2 A G—A 48 year old male suffered an acute attack of pneumonitis with fever chills productive cough and wheeze in April 1949 He was treated at home with penicillin but a chest x ray (Fig 2A) showed an irregular lesion in the *left* upper lung field *It was thought to be a carcinoma of the lung although bronchoscopy* and sputum studies for tubercule bacilli and tumor cells were negative At exploration of the chest on May 23 1949 a mass was found in the left upper lobe



Fig 2B

bronchi, both proximal and distal to the mass of cysts, were dilated



Fig 3A



Fig 3B

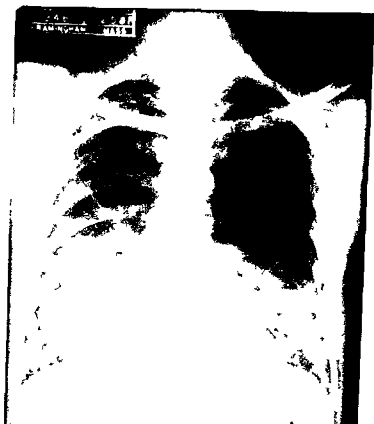


Fig 4A

Case 4 A B—This was a 40 year old veteran complaining of marked progressive dyspnea Chest x ray (Fig 4A) showed a huge bullous cyst filling over two-thirds of the left chest He was treated in September 1948 by introduction of a catheter into the cysts (Fig 4B) The catheter was connected to continuous suction of 16 cms of water negative pressure After 16 days the cyst was closed and the catheter withdrawn (Fig 4C) Dyspnea has remained improved and the cyst has not recurred after more than a year (Fig 4D)

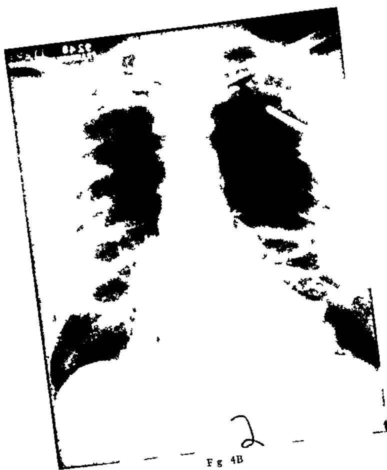


Fig 4B



Fig 4C

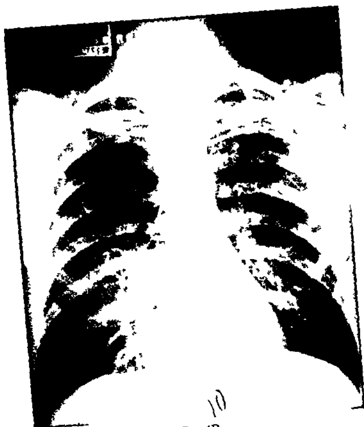


Fig 4D



Fig 5

Case 5 R I —This 36 year old male sustained a spontaneous pneumothorax on the right on August 29, 1947 There was no response to bed rest or repeated aspirations of air from the pleura Chest x-ray of September 4, 1947 showed a 70 per cent pneumothorax on the right (Fig 5) On exploration of the chest on September 22 small leaking subpleural blebs were found at the apex of the right upper lobe These were removed, the bases plicated, and the lung re-expanded He has remained well

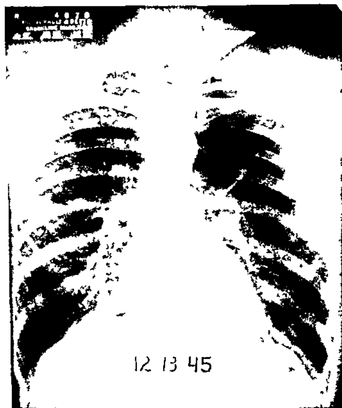


Fig 6A

Case 6 S S —This was a 26 year old veteran who was told that his chest x ray was abnormal when discharged from the Army in December, 1945 (Fig 6A) He had no symptoms and the linear density in the left upper lung field was difficult to interpret By September, 1945 (Fig 6B) a clear-cut giant cyst of the left upper lung field was made out He still had no symptoms and indeed worked as a saxophone player Exploration was advised and a giant cyst attached to the upper lobe was removed He has been well ever since

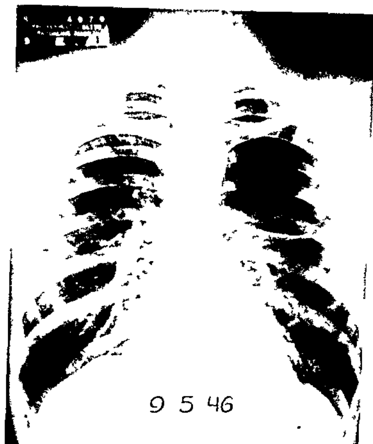


Fig 6B

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PULMONARY ARTERIOVENOUS FISTULA

(Cavernous Hemangioma of the Lung
Arteriovenous Aneurysm of the Lung)

By ANDREW L BANYAI, M D and J WINTHROP PEABODY, M D

This disease is characterized by multiple free intercommunications between the pulmonary artery and vein The lesion, as observed on post mortem examination or in the surgically removed specimen, consists of a group of lobulated, thin walled, saccular, blood filled spaces occupying limited areas of less than one lobe or the entire extent of one lobe Lesions may be present in both lungs of the same patient The maximum diameter of the aneurysmal sac may reach 8 cm The inner surface of the dilated vascular structures is covered with endothelium Churton (1897) is credited with the first report on its pathologic findings The first clinically identified case was recorded by Smith and Horton in 1939 In addition to changes in the pulmonary vessels, small hemangiomas may be found on the lung surface, adhesions may develop between the visceral and parietal pleurae and collateral circulation may be demonstrable between the lung and the chest wall Pulmonary arteriovenous aneurysm is a congenital, familial hereditary disease which is transmitted as a dominant penetrance

This disease is an uncommon one Adams and his associates (1944) reported having encountered only one case in more than 240 000 admissions at the University of Chicago Clinics during the preceding fifteen years and not a single recorded instance of it in more than 4 380 necropsies at the same institution According to Sisson and his associates, only one case was found in nearly 20 000 postmortem examinations at the Johns Hopkins Hospital up to 1945 Yater and his associates in a review of the literature found only 41 cases To this they added two cases of their own

Symptoms

Symptoms may be present from birth or develop during childhood and gradually become aggravated with the passing of years In some of the cases reported, the onset of symptoms was associated with severe respiratory infection, in others, medical attention was sought during the second or third decade of life The usual complaints are headache, dyspnea on exertion, thickness of speech dizziness, giddiness, episodes of syncope lasting for few minutes, convulsions, paroxysmal nocturnal dyspnea, substernal oppression and paresthesias in the arms These

symptoms are due to anoxia The latter is attributable to two factors 1 There is a shunt of large amounts of nonoxygenated blood from the pulmonary artery into the pulmonary vein From here it returns to the left side of the heart and to the arteries of the greater circulation 2 In consequence of shunting of large quantities of blood through the arteriovenous aneurysm, an insufficient supply of blood reaches the alveolar capillaries for physiologic oxygen carbon dioxide exchange The resulting symptoms may become so intense that the patient is doomed to complete invalidism unless proper treatment is instituted On the other hand, when the arteriovenous communication is small, these symptoms may be entirely absent This may be the case in a number of individuals with various degrees of teleangiectasia in the skin There are two other symptoms which should be mentioned One is frequent and rather inconsequential It is cough It may be complained of only when the patient is lying on the side of pulmonary involvement The other is more common and may have serious implications It is pulmonary hemorrhage Its provocative factor may be undue exertion which is bound to increase the blood pressure Fatal termination of the disease by such event has been recorded Incidental symptoms may result from phlebothrombosis and embolism in various parts of the body These individuals are predisposed to phlebothrombosis on account of the greatly increased values in the volume of the red blood cells

Special mention should be made of the case of Sisson and his associates Their patient was a Negro woman of 45 years of age The onset of symptoms was sudden nonradiating epigastric pain associated with severe dyspnea The same symptoms recurred every two weeks Subsequently dizziness and nausea accompanied the attacks and she became orthopneic The latter condition persisted Prior to admission to the hospital, she developed small pulmonary hemorrhages and numbness in the left arm Correct diagnosis was established clinically and confirmed on postmortem examination which revealed a large pulmonary arteriovenous aneurysm in the left lower lobe and a small one in the right middle lobe The patient of Rodes complained of dyspnea since early childhood and of jaundice of short duration He sought medical care on account of increased dyspnea Examination showed cyanosis, small hemangiomas on the lip, pronounced clubbing of the fingers, hemoglobin from 108 to 112 per cent and 7,540 000 red blood cells per cubic millimeter There were two medium sized round shadows in the lower one half of the left lung Subsequently, two massive hem-

orrhages occurred, one of them with instantaneous fatal termination Postmortem examination revealed typical arteriovenous aneurysm in both lungs

Diagnosis

The diagnosis of this disease is not difficult when one becomes aware of it through the history obtained and by the presenting symptoms and signs The family history may reveal the occurrence of nose bleeds or hemorrhages from the gastrointestinal tract It is well to inquire about the health history of grandparents and other known antecedents, for the peculiar tendency to epistaxis may skip one generation Also one may discover on close examination hemangiomas on the skin of the face, neck or trunk or their presence on the lips or buccal mucous membrane

On inspection, the most obvious findings are cyanosis, particularly that of the lips, face and hands and clubbing of the fingers and toes Relatives of the patient may state that cyanosis was not noticeable until school age or adulthood Maier and his associates suggested that the absence of cyanosis in these cases speaks in favor of a shunt from the bronchial arteries to the cavernous hemangioma It is well to keep in mind the possibility of arteriovenous aneurysm of the lung when there is pronounced clubbing of the fingers and toes without obvious heart disease, provided other conditions can be excluded which may bring about similar changes These include pulmonary abscess, bronchiectasis, primary and metastatic malignant tumors of the lung, extensive, long standing pulmonary fibrosis, chronic bronchitis, bronchial asthma, emphysema, pulmonary hemosiderosis, empyema, malignant tumors of the pleura, mediastinal tumors, congenital heart disease, subacute bacterial endocarditis, cachexia strumipriva, generalized amyloidosis, syphilis, chronic liver disease, chronic kidney disease, amebiasis, ulcerative colitis, intestinal polyposis and congenital familiar clubbing of the fingers

The patient may show signs of underdevelopment which is attributable to relative anoxia since birth Arteriovenous aneurysm of the lung may be suggested by hemangiomas of the skin (face, hand, neck and elsewhere) and of the mucous membranes (lips, nose, oropharynx) In some of the cases reported, physical examination revealed signs of pulmonary consolidation In most cases, a loud, blowing systolic or continuous murmur (bruit) is audible over the area of the lung where the arteriovenous aneurysm is localized The murmur is exaggerated

on inspiration It may not be detectable in patients with involvement of the entire lobe

Roentgenograms of the chest taken in the standard postero anterior, lateral and oblique positions show an irregular or round, oval or triangular dense shadow in one or both lung fields, located near the hilum or extending from the latter to the periphery in the form of a broad band of uneven density Fluoroscopic examination may reveal wide connection between the lesion and the hilar blood vessels and permits its separation from the heart shadow Pulsation of the lesion may be visualized on fluoroscopic inspection and by kymography in most instances Tomograms are of value in the accurate localization and demarcation of the involved area and its connection with the hilar region It was pointed out by Lindgren and confirmed by Makler and Zion (1946) that variations in the size of the lesion are demonstrable during fluoroscopic examination while the patient carries out the Valsalva and Mueller experiments They observed that there was a momentary decrease in the size of the lesion during forced expiration while the mouth is closed and the nostrils are occluded An increase in the size of the lesion was noted under the same circumstances during forced inspiration Bronchogram is helpful in the negative sense in that it demonstrates the absence of communication between the bronchial tract and the arteriovenous aneurysm Angiocardiography is a useful and safe procedure in expert hands for the roentgenologic visualization of the lesion Its technique is described in detail in the chapter on Sclerosis of the Pulmonary Arteries and Arterioles

Laboratory examinations contribute valuable pertinent information to the diagnosis There is a definite polycythemia The red blood cell count varies from 6 000 000 to 11 000 000 Polycythemia is absent in the cases where the arteriovenous communication is not too large Usually there is a marked increase in the number of blood platelets The blood volume may reach almost twice the normal figure, the increase being due to an augmentation in the number of erythrocytes (Normal values are from 72 to 100 cc per Kg of body weight) The hematocrit is found to be between 60 and 80 per cent (Normal 37 to 54 per cent) Hemoglobin values have been recorded as high as from 125 to 180 per cent of normal The oxygen saturation of the blood is far below normal

Electrocardiographic studies may reveal right axis preponderance.

Differential Diagnosis

In arriving at the correct diagnosis, due consideration should be given to ruling out conditions in which symptoms, signs and x ray findings may be similar to those of arteriovenous aneurysm of the lung These include various infections, bronchiectasis, congenital heart disease, pulmonary arteriolar sclerosis, Ayerza s disease, polycythemia vera and polycythemia due to noxious fumes and gases to emphysema, extensive pulmonary fibrosis of inflammatory origin or caused by the massive inhalation of harmful dusts, pulmonary intravascular thrombosis and pulmonary diseases casting similar shadows in the x ray films A list of the latter is given in the section on Pulmonary Adenomatosis

Prognosis

At the time when these patients seek medical attention, the prospect of their life expectancy is not too bright unless adequate surgical treatment is carried out There is the imminent hazard of grave perhaps fatal pulmonary hemorrhage and also, the possibility of death from cerebral or coronary thrombosis Of the four cases reported by Wodehouse one developed brain abscess on the basis of a minute and clinically unrecognized encephalomalacia which resulted from thrombosis secondary to polycythemia Myocardial strain with its possible harmful consequences is another liability In the case of Maier and his associates (1948), a super imposed bacterial endocarditis complicated the clinical picture

Treatment

There are effective and safe surgical methods available for the correction of this condition These are ligation of the feeder artery local excision of the lesion lobectomy and pneumonectomy Of these pneumonectomy and lobectomy seem to be the most efficacious Following these operations, there is a prompt improvement in the patient s subjective condition and a rapid disappearance of cyanosis is noted Postoperative changes in the blood are illustrated in the following table

TABLE I

Reported by	Type of Operation	RBC		Hemoglobin		Hematocrit		Arterial O_2 Saturation Percent	
		Before	After	Before Gm	After Gm	Before	After	Before	After
Adams et al (1944)	Pneumonectomy	7 200 000	5 200 000	23 0	15 7	82	34		
Goldman 1943	Pneumonectomy	7 900 000	4 470 000	26 0	13 6	79	45	70	100 0
Burchell et al (1947)	Lobectomy	7 590 000	5 180 000	24 1	14 8	82	48	74	94 1
Beierwaltes et al (1947)	Lobectomy	8 000 000	6 700 000	21 6	18 4	62	75	77	92 2
Maier et al (1948)	Lobectomy	6 900 000	4 400 000	22 0	13 0	70	36	74	96 0
Moyer et al (1948)	Pneumonectomy	8 200 000	5 100 000	22 8	15 0	60	42	63*	90 0
Ettinger et al (1949)	Lobectomy	6 320 000	4 490 000	17 9	12 5	61	44	79 9	
Yater, et al (1949)	Lobectomy	7 400 000	3 750 000	18 0	12 0	55	39		

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HEREDITARY HEMORRHAGIC TELEANGIECTASIA

By ANDREW L BANYAI, M D and J WINTHROP PEABODY, M D

The hereditary familial condition, also known as Rendu Osler-ber disease, is characterized by pin point to split pea sized vascular itations which occur most frequently in the skin and in the mucous nbrane of the respiratory passages, the gastrointestinal tract and the genito urinary system Less commonly, the conjunctiva and the meninges of the brain and spinal cord are involved The nasal mucous membrane is a favorite site of teleangiectasis Also, lesions have been observed on the mucosa of the lips, gingiva, tongue, palate, larynx, trachea, bronchi and at various locations in the gut According to the report of Kushlan (1946), there are 175 families, with more than 1,000 members on record, who are suffering from this disease

Pathologic examinations reveal that the teleangiectatic blood vessels are enclosed in thin walls which consist of a single layer of endothelium and epithelium One of the most characteristic features of this condition is a pronounced tendency to bleeding from the mucosal lesions Consequently, severe anemia may develop and may lead to chronic invalidism

The disease affects both sexes with about equal frequency and the hereditary factor is transmitted as a simple dominant by males and females to their offspring However, it is well to keep in mind that in some families, one or two generations may be skipped by the disease

We maintain that hereditary hemorrhagic teleangiectasia and arteriovenous fistula of the lung are structurally similar vascular malformations, but clinically, they represent two distinct entities The following points support this view

1 Hereditary hemorrhagic teleangiectasia involves only cutaneous and mucosal surface areas, whereas arteriovenous fistula of the lung is a disease in which large areas of one or more lobes are occupied by greatly dilated communicating blood vessels The size of the pulmonary vascular dilatation may be as much as 8 cm

2 Dyspnea, cyanosis and clubbing of the fingers and toes are common clinical manifestations of arteriovenous fistula of the lung These findings are absent in the usual forms of hereditary hemorrhagic teleangiectasia

3 Another distinctive difference between these two conditions is that groups of vascular dilatation in teleangiectasia have a tendency to

vary in their number and size at any given site and may completely disappear after a number of years Also, there are great variations in their tendency to bleeding in teleangiectasia

4 *Polycythemia*, increased hemoglobin and hematocrit are common sequels of arteriovenous aneurysm of the lung, but they are not encountered in hereditary hemorrhagic teleangiectasia

It is recognized that hereditary hemorrhagic teleangiectasia and arteriovenous fistula of the lung may occur simultaneously, for both are hereditary vascular hamartomas

When teleangiectasia is localized in the bronchial mucosa, the patient may complain of frequent, slight blood streaked sputum or of frank pulmonary hemorrhage Either of these manifestations may occur periodically, directly prior to menstruation The occurrence of such cyclic hemorrhages are attributable to coincidental congestion in the lung Fatal outcome from pulmonary hemorrhage has also been recorded in this condition

Diagnosis is established on the basis of relevant family history detection of teleangiectatic lesions in the skin and accessible mucous membranes, demonstrable teleangiectatic lesions in the gastrointestinal tract or the occurrence of otherwise unexplainable hemorrhage from the latter or from the genitro-urinary tract Moderate or severe anemia may be noted In some instances, hepatomegaly is found Teleangiectatic lesions may or may not be visualized in the larynx, trachea or bronchi on laryngoscopic and bronchoscopic examinations Negative bronchoscopic findings do not rule out the possibility of bronchial teleangiectasia It is known that the entirety of the inner surface of the bronchial tubes cannot be seen through the bronchoscope Roentgenograms of the chest are entirely normal in patients with bronchial teleangiectasia, except immediately after a major pulmonary hemorrhage In the latter instance, extravasated aspirated blood is likely to cast wide spread nodular shadows in the x ray film in one or both lungs These shadows may persist for several days or a few weeks

The differential diagnosis calls for distinguishing hereditary hemorrhagic teleangiectasia from diseases which may lead to pulmonary hemorrhage These include inflammatory changes in the bronchi or lung parenchyma (of bacterial, viral, rickettsial, parasitic, foreign body or other origin), broncholiths and pneumoliths neoplasms (benign or malignant, primary or metastatic), arteriolar sclerosis, pulmonary hypertension, perforated aneurysm (simple or arteriovenous), decom

pensated heart disease, pulmonary infarction, necrosis in pulmonary fibrosis due to noxious dusts, possible vitamin deficiency, essential pulmonary hemosiderosis and blood dyscrasias

Rutin was found by Kushlan to give encouraging results in this condition Rutin is a flavon glycoside which is prepared by extraction from buckwheat It is available in tablets of 20, 50 and 60 mg The usual dosage is from 20 to 60 mg three times a day A confirmatory case report was published by Schwartz and Armstrong in 1948 In addition, supportive measures are employed, with particular regard to the correction of the patient's anemia and any nutritional deficiency that may be present Koch and Escher reported two patients given estrogen or estrogen and androgen therapy combined, in whom in one to two weeks after treatment was started, a decrease in the incidence and severity of epistaxis was noted

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PULMONARY FEATURES OF TUBEROUS SCLEROSIS

By ANDREW L BANYAI, M D and J WINTHROP PEABODY, M D

Tuberous sclerosis is a congenital, hereditary systemic disease which may involve several organs and structures simultaneously, such as the central nervous system, skin, liver, spleen, kidneys, ovaries, suprarenals, bones, lymph nodes, the heart and the eye grounds The first case with identified lung changes was reported by Berg in 1938 Structurally, the lesion consists of embryonal cells either of muscular, connective, vascular or fat tissue It results from a developmental disturbance in the mesenchymal tissue Berg and Vejlens refer to a case described but not identified by Lutembacher in 1918 The latter noted unusual vascularization of the lung surface Also, Kveim and Berg and Nordeskjoeld recorded the angiomatous appearance of these lesions They mention the observations of Harbitz (1912) who found fibroangiosarcomatous alterations in tissues showing the characteristics of tuberous sclerosis The close relationship between tuberous sclerosis, angiomatoses and von Recklinghausen s disease has been commented upon by several clinicians The skin manifestations of tuberous sclerosis are known as adenomata sebacea sebaceous nevi, or Springle s disease and consist of yellowish red nodules

Tuberous sclerosis is usually encountered in children and young adults, sometimes in more than one member of the same family The disease is often associated with mental deterioration, idiocy or epileptic seizures Berg and Nordenskjoeld reported two cases of pulmonary tuberous sclerosis confirmed on postmortem examination Both patients belonged to the same family Interestingly, according to the history obtained, their mother and maternal grandfather had tuberous sclerosis of the skin

We quote the pulmonary findings as recorded by these authors "The pleural surface was dotted with evenly distributed small bullae up to the size of nuts the majority being as large as peas The cut surface resembled a sponge The lung tissue was interspersed with small cavities embedded in a thick, firm tissue The septa between the larger cysts often reached a thickness of one centimeter or more, but in that case they contained numerous minute cysts In some places the walls of the cysts were as thin as paper, so that here and there a system of continuous cysts, separated by incomplete septa was formed No arrangement of cysts along the ramifications of the bronchial tree could

be observed The microscopic examination showed that only small remnants of the normal parenchyma of the lung remained For the rest, the picture was covered with cyst-like cavities of very different size and deficient in epithelial covering Most of the cysts were round in shape, others shrunken like bags or drawn out into a branching system of passages The walls of the cysts were for the most part made up of connective tissue, having an unmistakable character of tumor tissue of embryonic character ' In another case, in addition to the cystic pattern, they observed the following findings

(1) Alveoli filled with blood and hemosiderin

(2) Fibrous induration rich in blood vessels and associated with partly angiomatous formations

(3) Complete and extensive angiomatous new formations

The latter were observed as angioma simplex and also as enormously dilated thin walled blood cysts They note that "the angioma components do not occur in distinct nodes but filter out into the collapsed pulmonary tissue between vessels and bronchi of normal appearance The angioma tissue mixes intimately with the myomatous new formations" Unilateral or bilateral spontaneous pneumothorax may complicate the picture

Symptoms

The salient clinical features of pulmonary tuberous sclerosis are recurrent spontaneous pneumothorax, repeated pulmonary hemorrhages and gradually increasing dyspnea

Diagnosis

Careful investigation of the family history is mandatory It is essential closely to examine the skin and the central nervous system, with particular reference to psychopathic inferiority and epilepsy Special attention should be paid to examination of the eye grounds, lymph nodes and bones X-ray studies of the latter may reveal changes which resemble those found in hyperparathyroidism with osteitis fibrosa cystica, sarcoidosis (osteitis tuberculosa cystoides), Albright's syndrome and Ollier's disease Roentgenograms of the chest show delicate, net-like or honeycomb appearance in both lung fields There are a great many areas of increased radiotranslucency the size of which varies from that of a millet seed to hazelnut. In the case of Dos Santos and Wohlwill, the cysts reached very large size Tomography is of value for the definitive demonstration of the cysts

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Tuberous sclerosis is a congenital, hereditary systemic disease which may involve several organs and structures simultaneously, such as the central nervous system, skin, liver, spleen, kidneys, ovaries, suprarenals bones, lymph nodes, the heart and the eye grounds The first case with identified lung changes was reported by Berg in 1938 Structurally, the lesion consists of embryonal cells either of muscular, connective, vascular or fat tissue It results from a developmental disturbance in the mesenchymal tissue Berg and Vejlens refer to a case described but not identified by Lutembacher in 1918 The latter noted unusual vascularization of the lung surface Also, Kveim and Berg and Nordeskjoeld recorded the angiomatous appearance of these lesions They mention the observations of Harbitz (1912) who found fibroangiosarcomatous alterations in tissues showing the characteristics of tuberous sclerosis The close relationship between tuberous sclerosis, angiomatoses and von Recklinghausen s disease has been commented upon by several clinicians The skin manifestations of tuberous sclerosis are known as adenoma sebacea, sebaceous nevi, or Springle's disease and consist of yellowish red nodules

Tuberous sclerosis is usually encountered in children and young adults, sometimes in more than one member of the same family Th disease is often associated with mental deterioration, idiocy or epilept c seizures Berg and Nordenskjoeld reported two cases of pulmonary tuberous sclerosis confirmed on postmortem examination Both patient belonged to the same family Interestingly, according to the history ob tained, their mother and maternal grandfather had tuberous sclero of the skin

We quote the pulmonary findings as recorded by these autho "The pleural surface was dotted with evenly distributed small bull up to the size of nuts, the majority being as large as peas The cut sur face resembled a sponge The lung tissue was interspersed with sma cavities embedded in a thick, firm tissue The septa between the larg cysts often reached a thickness of one centimeter or more, but in th case they contained numerous minute cysts In some places the wal of the cysts were as thin as paper, so that here and there a system continuous cysts, separated by incomplete septa was formed No rangement of cysts along the ramifications of the bronchial tree cou

COLLAGEN DISEASES OF THE LUNG

PLEUROPULMONARY MANIFESTATIONS OF LUPUS ERYTHEMATOSUS

By ANDREW L BANYAI, M D and J WINTHROP PEABODY, M D

KLEMPERER and his associates (1941) were the first to point out that the pathologic changes in the connective (collagenous) tissue as a bodily system are the cardinal manifestations of lupus erythematosus They recognized that morbid alterations which occur in this disease consist of two components

1 Cellular reaction within the connective tissue,

2 Changes in the fibrillar elements (fibers) and in the amorphous ground or cement substance Although they admit that either of these two components may reflect pathologic changes, they noted that consistently the most prominent finding was the fibrinoid transformation of the collagenous fibers and ground substance They emphasized that this fibrinoid metamorphosis represented a profound change in the physico-chemical state of the colloid connective tissue and that it was sufficient in itself to offer a plausible explanation for well defined morphologic and chemical changes characteristic of this disease These changes are identified as straightening and thickening of the collagen fibers, their apparent friability, localized eosinophilia and refractibility, together with visible increase in the ground substance and its density Also, there is evidence of heavy local infiltration by polymorphonuclear leucocytes and lymphocytes and of degenerative changes such as pyknosis and nuclear fragmentation of the fixed connective tissue cells, fibroblasts and histiocytes In this connection, there are two points of utmost importance from the diagnostic as well as from the prognostic standpoint

(1) Localized colloidal imbalance of the connective tissue of certain organs may cause symptoms without clinically demonstrable structural deviation from normal

Cysts resulting from tuberous sclerosis may be found on x ray examination of the chest in persons without complaints

Late in the course of the disease, signs of hypertrophy of the right ventricle, right axis deviation in the electrocardiogram, plethora of the face and polycythemia are observed The diagnosis is supported by finding adenomata sebacea in the face or elsewhere

Prognosis

Fatal termination can be anticipated in several years, usually before the patient reaches middle age Death may result from cerebral hemorrhage

Treatment is symptomatic and supportive

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matory cells first appeared in the interalveolar tissue and eventually encroached upon the alveoli and collapsed them or whether the alveoli were the seat of early changes As the lung is observed in its present state, there is a lobular consolidation and the intervening air-containing alveoli are surrounded by thickened alveolar septums in which there is a low grade chronic inflammation The inflammatory cells are almost universally of the mononuclear type, some are doubtless lymphocytes, a few are plasma cells, but the most characteristic and, of course, most conspicuous, is a large mononuclear cell containing a deeply stained nucleus usually somewhat eccentrically placed and surrounded by a wide zone of slightly pinkish staining cytoplasm As the more consolidated areas are approached, this inflammatory reaction becomes more extensive and brings about a collapse of the alveoli In these more affected areas alveolar walls have disappeared and the lung tissue appears as a solid inflammatory mass in which the larger blood vessels are still identifiable In some reas in which the destruction is not so far advanced, hyalin plugs occur in the compressed alveoli "

Other postmortem reports have emphasized the occurrence of fibrinoid degeneration in the perivascular and peribronchial tissues, hyalin thickening of the alveolar walls which show a "wire loop appearance, a typical renal finding in this disease, hyalin necrosis in the pulmonary vessels, and numerous hemorrhages up to 1 cm in diameter Teilum (1948) considers the pneumonic and hemorrhagic alterations as a morphologic expression of an allergic tissue reaction The latter, in certain of its phases, may parallel the allergic phenomenon of Arthus Also, Teilum observed the simultaneous occurrence of hyperglobulinemia, paramyloidosis and hyalinosis of the reticuloendothelial system in disseminated lupus erythematosus

Pulmonary consolidation may develop without skin lesion being present It may be detectable after the disappearance of the erythema It may shift from one lobe to another or from one lung to the opposite side within a few weeks It may disappear entirely, only to recur a few weeks or a few months later Also, it may completely clear before death

Pleural involvement is common in lupus erythematosus The pleurisy may be plastic or exudative, unilateral or bilateral Pathologic examinations show that the pleura is thick, opaque, with numerous petechial

(2) Colloidal imbalance of the connective tissue is a reversible condition This implies the possibility of the complete disappearance of clinically significant pathologic changes in some of the organs

The first clinical description of lupus erythematosus by Hebra dates back to more than a century Its present name was coined by Cazenave in 1851 Kaposi first noted general and systemic manifestations of this disease in addition to the skin rash Osler emphasized the importance of visceral involvement in lupus erythematosus and Libman and Sacks first called attention to an unusual form of endocarditis in this condition

Lupus erythematosus is a toxic state with prolonged fever and with a remittent cachectic course The latter lasts from several weeks to several years It is more common in the white race than in Negroes From 60 to 80 per cent of the patients are women, the highest incidence being during the third and fourth decades of life It has protean manifestations, the dominant characteristics of which are predicated upon the site of major organic involvement Two types of skin lesion are distinguished One is the discoid, benign form with "butterfly eruption over the bridge of the nose and malar prominences The other is the acute disseminating form which has a tendency to spread all over the face, ears, arms, chest and subsequently, virtually all over the body According to Belote these two forms are only different phases of the same disease Visceral lesions have been observed in association with the acute, disseminated type It is well to remember, however, that visceral diseases may precede skin lesions by months As a matter of fact, in some instances, skin erythema does not appear until shortly before death In view of this, it is reasonable to say that the skin erythema of lupus erythematosus is in some cases only an external but in consequential part of the clinical syndrome

Localized forms of the disease include polyarthritis, polyserositis (pleurisy, pericarditis, peritonitis), endocarditis, nephritis, lymphadenopathy, retinitis, cerebral involvement and pulmonary involvement The latter may appear in two forms

1 Miliary nodules
2 Pneumonic consolidation

An excellent description of histologic findings in the lung recorded by Rakov and Taylor is worth quoting

"In the more consolidated areas it is almost impossible to say how the consolidation developed, i e, whether the inflam

diagnosis He may complain of having a vague illness of long duration or relates recurrent febrile episodes, or gives a history of attacks of rheumatism ' These conditions may or may not have been associated with a dusky red erythema on the face, the onset or exacerbation of which often follows prolonged, intense exposure to sunlight The facial erythema usually extends to the neck, extremities, hands and trunk when visceral lesions are present, but the occurrence of cutaneous and internal organic involvements are not necessarily simultaneous Diffuse alopecia is common Occasionally, one finds enlarged cervical or other superficial lymph nodes

Physical examination of the chest is negative when the pulmonary lesion consists of miliary nodulations One can elicit the usual signs in cases with pneumonic consolidation Roentgenograms of the chest should be taken on repeated occasions during the course of the disease on account of the changeability and reversibility of some of the pathologic manifestations The roentgenologic findings vary from slight accentuation of the hilar structures and bronchovascular markings to widespread miliary nodulation and pneumonic consolidation The latter may reveal a migratory tendency

Pleural involvement is recognized by the presence of friction sound or by the characteristic signs of effusion It is well to keep in mind that the roentgenogram of the chest may be entirely normal while clear cut friction sounds are detected over large areas When pleural effusion is suspected, exploratory thoracocentesis should be done The fluid withdrawn from the pleural cavity may be serous, sanguineous or a transition between the two The character of the fluid may change alternatingly from serous to sanguineous or vice versa between chest aspirations The pleural effusion shows all the earmarks of an inflammatory exudate, with a low polymorphonuclear cell count It is negative bacteriologically

Reversal of the albumin globulin ratio of the blood serum was recorded by Coburn and Moore in all of their patients with disseminated lupus erythematosus It was brought about by an increase of the gamma and euglobulin fractions The total serum protein was normal Also, Thyresson noted that hyperglobulinemia is a constant phenomenon in lupus erythematosus of the disseminated type

Hematologic examinations show leucopenia as a rule, which may be as low as 2,000 per cubic millimeter The differential count of the white blood cells is normal With pneumonic consolidation, the white

hemorrhages throughout Teilum described miliary granulomata and nodular necrosis in the parietal and visceral pleurae These changes are *seen in the* form of clustered grayish white nodules which resemble *tubercles* Pleural changes may be associated with, or followed by pulmonary consolidation, but frequently occur without it *The effusion* is clear, transparent, serous, serosanguineous or sanguineous

The etiology of this disease has not been definitely established It is entirely possible that it is an allergic condition in which the pathologic changes are brought about by hypersensitiveness to *bacterial products,* as proposed by Stokes So far, no pathogenic micro organisms have been *recognized* as causative *factors in its pathogenesis* Gerlach *was able* to demonstrate experimentally fibrinoid transformation of collagen *tissue in allergic reactions Jaeger and Roessle consider such changes* characteristic and constant manifestations of allergic diseases Klemperer, who has *contributed so substantially to the identification of this* disease, expressed serious doubts about lupus erythematosus being solely *and invariably attributable to hypersensitivity*

Symptoms

Symptoms of visceral collagen disease related to lupus erythematosus show great variations The patient is likely to have acute bouts of chills and fever This latter may reach from 104° to 105 F (40 to 40 5° C) and is associated with profuse perspiration, malaise and loss of weight The fever may level off at 100° F, disappear in several weeks and recur again with new manifestations of visceral involvement Pleuropulmonary lesions are usually accompanied by pain in the chest, which is exaggerated on deep inspiration Also, cough and expectoration of mucoid sputum are noted Dyspnea may be due to pulmonary consolidation, acute fibrinous pleurisy, large unilateral or bilateral pleural effusion or to endocardial or pericardial changes Blood tinged sputum and frank pulmonary hemorrhage may be seen These are brought about by degenerative connective tissue changes in the adventitia of th pulmonary vessels, particularly in the capillaries The term visceral angiitis, introduced by Krupp in 1943, is well applicable to the condition Other symptoms include abdominal pain, nausea, diarrhea, joint pains with swelling and tenderness but without redness Not infrequently, there is a tendency to oral and nasal bleeding

Diagnosis

The past history of the patient *may offer an important clue* to the

Infected congenital miliary cysts
Fungus infection
Residuals following pulmonary hemorrhage
Pulmonary hemosiderosis
Miliary form of Hodgkin's disease
Multiple widespread small pulmonary infarctions
Residual iodized oil after a bronchogram
Pulmonary congestion due to heart failure
Kaposi's disease
Lipoid pneumonia
Lymphatic leukemia
Paragonimiasis
Periarteritis nodosa
Polycythemia vera
Purpura hemorrhagica
Sarcoidosis
Schistosomiasis
Silicosis and other pneumonoconioses
Syphilis in the form of miliary gummata
Tropical eosinophilia
Miliary tuberculosis
Primary essential xanthomatosis

When exploratory thoracocentesis reveals clear, serofibrinous pleural effusion, one should consider the possibility of other diseases where similar finding obtains These are tuberculosis, bronchopneumonia and lobar pneumonia of bacterial, rickettsial or viral origin, rheumatic fever, trauma, trichinosis, nephritis, gout, transdiaphragmatic spread of subdiaphragmatic infections, myeloid and lymphatic leukemia, primary and metastatic tumors of the lung, Hodgkin's disease and infestation with echinococcus

Other diseases in which sanguineous effusion may occur include primary or metastatic carcinoma, thoracic lymphosarcoma, Hodgkin's disease, thoracic lipoma, malaria, pulmonary infarction, early infection with streptococci, rheumatic fever, influenza, pneumococcus pneumonia, smallpox, typhoid fever, scurvey, blood dyscrasias, such as thrombocytopenic purpura and leukemia, chronic nephritis, Banti's disease, massive atelectasis, syphilis and tuberculosis.

blood count varies from 7,000 to 30,000, rarely, it may reach 50,000 per cubic millimeter

Hargraves and his associates demonstrated so-called lupus erythematosus cells (L E cells) in concentrated specimens of the bone marrow of patients who had acute lupus erythematosus Also, Hargraves and Haserick and Bortz observed that the plasma of these patients contained some specific factor The latter when added to bone marrow material of normal persons, induced clumping of the leucocytes into rosettes and led to the formation of characteristic, inclusion containing L E cells

The sedimentation rate of the erythrocytes is accelerated

Lupus erythematosus is one of the conditions in which the occurrence of false positive tests for syphilis have been observed Coburn and Moore noted that the gamma globulin of the blood serum of these patients became readily attached to phospholipids of the antigen used in the Wassermann and Kline tests This may be interpreted as signifying that gamma globulin is essentially an immune body

In the differential diagnosis of this disease, one is obliged to rule out conditions which may lead to pulmonary consolidation, with or without pleural effusion These include tuberculosis, bacterial, rickettsial, protozoal, parasitic and virus infections Also, one should exclude lung abscess, acute interstitial pneumonitis, Loeffler's syndrome and pulmonary adenomatosis When collagen disease of the lung is associated with miliary shadows in the roentgenogram, it should be distinguished from the following conditions

- Miliary abscesses
- Pulmonary acariasis
- Pulmonary adenomatosis
- Miliary amyloidosis
- Bagasse disease
- Beryllıosis
- Bronchiolitis
- Miliary bronchopneumonias, including certain forms of virus infection
- Bouillaud s disease
- Extensive nodular calcifications in renal dwarfism
- Cave sickness
- Miliary carcinomatosis and similar metastatic tumors
- Other collagen diseases, such as scleroderma
- Eosinophilic leucocytosis

disease, the therapeutic response was excellent or good in 15 (65 per cent)

Additional management of the patient should consist of bed rest, high caloric diet with adequate vitamin intake, supportive measures, such as intravenous injections of dextrose solution or repeated transfusions of whole blood, symptomatic measures, such as medication for the relief of chest pain, gastro-intestinal and other symptoms, inhalation of oxygen for the relief of dyspnea, inhalations of a mixture of 5 per cent carbon dioxide and 95 per cent oxygen as an expectorant when considerable inflammatory exudate is present in the lung and its expectoration is difficult Removal of pleural effusion is mandatory when its accumulation interferes with the normal respiratory function of the lung In some instances, repeated bilateral chest aspirations are necessary

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Prognosis

The visceral forms of this disease carry an unfavorable prognosis. Mortality in the subacute form is about 50 per cent and in the acute forms it is nearly 90 per cent The patient may die of azotemia bronchopneumonia meningitis or from other serious organic involvement

Treatment

Thorn and Bayles and Elkinton and his associates reported rapid remission of signs and symptoms in *acute disseminated lupus erythematosus* following treatment with pituitary adrenocorticotropic hormone (ACTH) Effective dose of this drug is from 75 to 160 mg given intramuscularly per day Elkinton and his co workers noticed that as the result of stimulation of the adrenal cortex during the initial phase of treatment with pituitary adrenocorticotropic hormone, there were fall in the eosinophilic leucocytes, sodium retention retention or loss of potassium occasionally negative nitrogen balance and increased excretion of urinary corticoids or 17 ketosteroids

Baehr recommends ACTH, 0 025 Gm every six hours intramuscularly, or cortisone, 0 15 to 0 20 Gm daily in two divided doses for a week or ten days then gradually reducing the daily dose every two or three days until a maintenance dosage is reached below which clinical activity occurs Further reduction is attempted in another two or three weeks A small maintenance dose for an indefinite period may be required by some patients as low as 0 05 Gm of cortisone once daily or every second day or 0 01 Gm ACTH twice daily

Johnson and Meyer reported nine cases treated with cortisone with decrease in symptoms and signs of the disease but relapse always followed cessation of therapy Irons and his associates noted in 13 cases pituitary adrenocorticotropic hormone produced quicker remissions than cortisone, but was followed by a higher incidence of complications The treatment is not a cure One patient died after long term therapy of complications and another died, apparently after insufficient initial therapy

Burgess and Pritchard found that cutaneous manifestations of this disease responded well to the administration of mixed tocopherols (Natopherol, Abbott) given in doses of 100 to 600 mg per day

Zarafonetis treated patients with lupus erythematosus with PABA (para aminobenzoic acid a member of the vitamin B group) Of 23 patients with acute, subacute and chronic disseminated forms of the

disease, the therapeutic response was excellent or good in 15 (65 per cent)

Additional management of the patient should consist of bed rest, high caloric diet with adequate vitamin intake, supportive measures, such as intravenous injections of dextrose solution or repeated transfusions of whole blood, symptomatic measures, such as medication for the relief of chest pain, gastro-intestinal and other symptoms, inhalation of oxygen for the relief of dyspnea, inhalations of a mixture of 5 per cent carbon dioxide and 95 per cent oxygen as an expectorant when considerable inflammatory exudate is present in the lung and its expectoration is difficult Removal of pleural effusion is mandatory when its accumulation interferes with the normal respiratory function of the lung In some instances, repeated bilateral chest aspirations are necessary

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PULMONARY DISEASE ASSOCIATED WITH SCLERODERMA

By Andrew L Banyai, M D and J Winthrop Peabody, M D

On the basis of increasing experience, it is becoming more and more evident that scleroderma is not a disease entity, but only one of the many possible manifestations of a systemic affection The latter may involve various organs and structures of the body to greater or lesser extent, whether these characteristic pathologic changes and their sequels are recognized clinically or not As early as 1898, Notthafft described pulmonary findings in addition to involvement of other internal organs, in association with scleroderma One of the recently recorded cases of scleroderma with pulmonary manifestations was reported by Spain and Thomas Clinical as well as pathologic observations have been recorded in connection with scleroderma, with reference to the kidneys, liver, gastro intestinal tract spleen, endocrine glands, myocardium, skeletal muscles, fascia, tendons and bones

Klemperer and his associates consider scleroderma (also known as chorionitis, dermatosclerosis, hidebound disease, morphoea and sclerema adultorum), a disease of the collagen of the connective tissue It is characterized by two components

(1) Fibrinoid degeneration

(2) Increase in the bulk and density of the mucoid ground substance of the connective tissue, together with fiber formation (sclerosis) and with or without proliferation of fibroblasts They emphasize the need of accepting connective tissues of the body as a well defined, widely dispersed colloidal system with its own peculiar diseases Fibrinoid degeneration of the connective tissues was found in scleroderma by Masugi and Ya, Pollack and Bevans On the basis of histologic studies, Goetz, maintains that the typical lesions in this disease are not due to fibrinoid metamorphosis of the connective tissue collagen Also, in view of visceral changes being an integral part of scleroderma, he proposed discarding the latter term and using a more suitable technical term instead, namely, progressive systemic sclerosis

Following the observations of Lewin and Heller who found pulmonary fibrosis in 8 per cent of their cases, and of Notthafft, macroscopic and microscopic findings in the lung were described by Matsui, Kraus, Weiss and his associates and others. The significant findings were

(1) Extensive proliferation of the connective tissue
(2) Thickening of the alveolar walls and interalveolar septums
(3) Marked vascular congestion in some areas
(4) Presence in the alveoli of many mononuclear cells filled with hemosiderin
(5) Marked proliferation of the arterial intima leading to complete occlusion of some of these vessels
(7) Compensatory emphysema
(8) Moderate thickening of the pleura with dense connective tissue.

Getzowa noted, in addition to diffuse alveolar fibrosis, cystic metamorphosis of the lung in two cases studied postmortem Cystic changes expanded from a wide subpleural base in a tapering manner toward the hilum, but not extending to the latter site The involvement was most intense in the lower and middle lobes The cystic areas were of firm consistency The individual cysts, varying from pea-sized to bean sized, were closely packed, separated from each other by narrow septums and had gray, shining walls In some places, closely packed cystic formations showed an adenoma like complex In other areas, gross appearance of carnification was evident in the form of nodules from 1 to 15 mm in size Microscopic inspection revealed that the epithelium of the cysts had a diffuse, uniform layer of cuboidal or short columnar, occasionally *high columnar cells Detached epithelial ribbons were common* With the disappearance of the parenchymal tissue, there was bronchiolar proliferation which later underwent cystic distention, designated as "cystic bronchiolar hyperplasia" In the intermediary zone, between cystic and noncystic areas of the lung, there was a transformation of the alveolar septal wall into acollagenous hyaline structures, with cessation of capillary circulation, disappearance of the capillaries, elastic fibers, and entire alveolar walls by autolysis Tears in the adjacent alveolar walls, similar to those seen in emphysema, were observed Even the noncystic segments of the lung showed pathologic changes, such as thickening of the alveolar walls due to congestion in the capillaries and fibrosis

The pathogenesis of scleroderma has not been as yet clarified Its possible endocrine origin (with possible implication of the thyroid, parathyroid or suprarenal gland) is suggested by its incidence being twice as high in the female as in the male Also, the frequent evidence of decreased ovarian function speaks in favor of such an assumption Because fibrinoid changes in the collagen of the interstitial tissues occur in allergy, some investigators are inclined to believe that generalized sclero-

derma is of allergic origin Klemperer expressed an opposite view He points out the fallacy of the *"post hoc ergo propter hoc"* reasoning of the claim relative to allergy as the fundamental cause of this disease In this connection, reference is being made to the occurrence of fibrinoid collagen changes in a variety of infections, such as syphilitic gumma, tuberculosis and diphtheria as recorded by Schosnig, in pathologic altera tions which result from physical or chemical irritants and at the base of peptic ulcer as noted by Askanazy Wuerthele Caspe and her associates found short, thick, acidfast bacilli in five proved cases of scleroderma They were able to isolate this micro-organism from the sputum, blood, nasal and subcutaneous tissue and were able to culture it from the blood in Dubos' medium Full growth was noted in two weeks They are of the opinion that this bacillus, tentatively named sclerobacillus Wuerthele Caspe, is a newly recognized member of the family of mycobacteriums and that it is the causative agent of this disease

Scleroderma occurs most commonly during the fourth and fifth decades of life, but it may be encountered at any age period from infancy to old age Not infrequently, it is preceded by polyarthritis or Raynaud s disease The latter also may have a simultaneous occurrence or it may develop subsequent to scleroderma As a matter of fact, Raynaud him self in 1862, was the first to report on scleroderma of the fingers in the disease bearing his name The course of scleroderma may take years On the other hand, there are cases where fatal termination ensues within a few weeks

The typical skin lesion is characterized by edematous, indurated, thick shiny, 'hide bound' appearance, with waxy yellow or ivory like color or with brown pigmentation not unlike that seen in about 80 per cent of patients with Addison's disease Occasionally, there is a circum scribed loss of normal skin pigmentation in other parts of the body surface The thickening of the skin results in its tightness, with consequent limitation in motion of the involved parts. Cutaneous *manifestations* of scleroderma may be found on the face, extremities, or over the entire body

Symptomatology

Superficial as well as organic involvement in scleroderma may be associated with general symptoms, such as occasional *moderate* elevation of the temperature, malaise, undue fatigue and palpitation Loss of weight may amount to as much as 20 lb (9 Kg) Symptoms referable to the chest are cough, pain in the chest and dyspnea The cough is either dry

or it is productive of scant, watery or mucoid sputum When considerable cardiac involvement is present, the sputum is likely to contain numerous mononuclear cells loaded with hemosiderin Pain in the chest may originate from two sources it is either due to pleural changes or to involvement of the intercostal muscles The latter together with marked fibrosis of the skin over the trunk may interfere with the normal respiratory expansions of the chest Dyspnea is attributable mainly to progressive, widespread interstitial fibrosis, decrease in the lumen or occlusion of pulmonary vessels and loss of respiratory surface or through destruction of alveolar walls and through obliteration of alveoli by over growth of connective tissue Dyspnea is bound to be exaggerated by extensive myocardial involvement Hydrothorax is a common complication of heart failure in these cases and it is likely to contribute to the patient's respiratory embarrassment Orthopnea and attacks of cardiac asthma have been noted in patients with progressive sclerosis of the heart muscle Occurrence of other symptoms is predicated upon the presence of serious implication of other organs and structures by this process Thus, one may find manifestations of stricture of the esophagus, stenosis of the bowel and other symptoms

Diagnosis

Reference has been made to characteristic skin changes In case of doubt, biopsy is the best means to confirm the diagnosis Typical findings are disappearance of the subcutaneous fat tissue and excessive increase in the fibrous tissue of the skin In advanced pulmonary cases, cyanosis is obvious It is an expression of anoxia which results from the aforementioned pulmonary lesions Cyanosis is more marked in patients with concurrent progressive myocardial sclerosis and also in those in whom cor pulmonale develops as the result of pulmonary fibrosis and associated increased circulatory resistance in the pulmonary vessels The respiratory motion may be limited on account of involvement of the thoracic muscles The percussion note is impaired over the lower two thirds of the chest in patients with extensive pulmonary lesion Simultaneously, signs of compensatory emphysema may be detected over less affected segments The breath sounds are either normal or diminished over the lower two thirds of the lung In case of failure of the left side of the heart, signs of hydrothorax may be observed and corroborated by exploratory thoracocentesis Also, enlargement of the heart may be detectable on physical examination Matsui recorded postmortem evidence of hypertrophy and dilatation of the right ventricle The pulmonic

second sound is accentuated on account of the increased resistance to the free circulation of blood in the narrowed channels of the pulmonary vessels Enlargement of liver and edema of the lower extremities are found with right sided heart failure. Other objective findings may be encountered when there is severe involvement in other organs

Roentgenologically demonstrable miliary calcifications throughout both lungs were first reported by Puddu in a patient with scleroderma with calcinosis, known also as Thibierge Weissenbach syndrome Murphy and his associates described pulmonary fibrosis seen in the roentgenogram of a patient with scleroderma The fibrotic changes present a network like pattern or a uniform ground glass appearance Heaviest changes are observed in the middle and lower one thirds with thinning out toward the apex They induced a diagnostic pneumothorax and in this manner were able definitely to establish that the fibrosis was in the lung and not in the soft tissues of the chest wall There are instances where one finds small nodular or mottled shadows on the roentgenogram in the lower two-thirds of the lung Negative x ray findings do not rule out pulmonary fibrosis The latter may be demonstrable on necropsy, as shown by Bevans, while roentgenograms are without significant pathologic changes X ray examination of the chest also enables one to ascertain the presence or absence of enlargement of the heart

Electrophoretic measurements carried out by Walker and Benditt showed no change in the total proteins of the blood, but there were an increase in the globulin and decrease in the serum albumin

In the differential diagnosis of pulmonary changes associated with scleroderma one should take into consideration the possibility of pulmonary congestion, congenital cystic disease of the lung, bronchiectasis, lipoid pneumonia and all conditions associated with widespread small nodular shadows on the chest roentgenogram For the list of these lesions the reader is referred to the chapter on Pulmonary Manifestations of Lupus Erythematosus Widespread miliary calcifications may be found in both lung fields in healed tuberculosis, fungus infection (aspergillosis, blastomycosis, coccidioidomycosis, histoplasmosis, moniliasis) ascariasis, certain cases of mitral stenosis renal dwarfism and essential intra alveolar microlithiasis (microcalcinosis)

The prognosis of progressive systemic sclerosis is unfavorable

Treatment

Symptomatic and supportive treatments should be augmented

by one of the measures known to be useful in the management of purely cutaneous forms of this disease Sellei (1932) assumed that there is deficiency in ferments in scleroderma and therefore he recommended the administration of tablets containing the three ferments of the pancreas namely trypsin amylase and lipase or raw pancreas 3½ ounces (100 Gm) daily, with or without the addition of duodenal ferments or liver extract in tablet form and by injection Rothman and Walker of the University of Chicago tried the feeding of raw pancrea and the administration of potent pancreatic extracts extensively without noticeable therapeutic benefits Greenbaum obtained favorable results from 15 grains (1 0 Gm) of ammonium chloride three times daily together with the intake of large amounts of table salt Others advocated cod liver oil viosterol and dehydrotachysterol Cod liver oil is given in doses of one half ounce (16 cc), viosterol in doses of 15 to 25 drops and dehydrotachysterol in doses of five drops three times daily Wuerthele Caspe and her associates having found acid fast microorganism (not tubercle bacilli) in the sputum and blood of these patients resorted to the administration of promin (sodium diaminodiphenyl sulfone didextrose sulfonate) which has been effectively used in experimental tuberculosis of guinea pigs The drug is given either orally in doses of 1 Gm (15 grains) daily or in gradually increasing doses intravenously For the latter purpose the initial dose is 0 2 Gm (3 grains) a day It is gradually increased to 2 0 Gm (30 grains) a day In one of their cases Jarisch Herxheimer reaction like response was observed Improvement was observed by Zarafonetis from the administration of PABA (para aminobenzoic acid) Preferably, it is given in tablet form as sodium para aminobenzoate or as a 10 per cent solution of potassium para aminobenzoate Both salts are given orally in doses of one to four grams at intervals of two to three hours

Evans and his associates summarized their therapeutic experience with 38 patients suffering from scleroderma as follows Definite improvement was seen with large doses of diphenylhydramine (benadryl) Similar results were recorded in patients treated with chloramphenicol (chloromycetin) and oxytetracycline (terramycin) Only one patient in a group of 14 responded favorably to para aminobenzoic acid Occasional transitory amelioration was noted with corticotropin (ACTH) and cortisone Improvement in esophageal and skin lesions was observed from the use of testosterone given by injection No therapeutic benefits were derived from the administration of alpha

tocopherol, glucosulfone sodium (promine), vitamin C, nicotinic acid, ergosterol, bismuth sodium triglycollamate, erythryl tetranitrate and priscol (2-benzyl-2-imidazoline)

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RHEUMATIC PNEUMONIA

(See respective chapter)

PERIARTERITIS NODOSA WITH PULMONARY INVOLVEMENT

(See respective chapter)

CHAPTER XIX

MISCELLANEOUS DISEASES OF THE LUNG

THORACIC MANIFESTATIONS OF DISEASES OF THE HEMOPOIETIC SYSTEM

By ANDREW L BANYAI, M D and J WINTHROP PEABODY, M D

DISCUSSION of this subject will be limited to involvement of the mediastinum, lung and pleura in association with lymphatic (lymphogenous) leukemia, myeloid (myelogenous) leukemia, plasmacytoma and polycythemia vera

Lymphatic Leukemia

It is the consensus that mediastinal lymph nodes are frequently affected during the course of chronic lymphogenous leukemia In a number of instances, groups of lymph nodes in this region may be transformed into a tumor like mass of considerable size Such development carries the potential danger of disturbing pressure upon the neighboring structures Consequently, the trachea may be partially compressed or one of the large bronchi occluded The latter may result either in atelectasis or emphysema of the corresponding area of the lung Also, pressure of the leukemic lymph node mass may obstruct the free current of chyle in the thoracic duct or interfere with the venous return through the large thoracic vessels These changes are likely to lead to the development of pleural effusion or to superior vena caval syndrome In some cases, chylothorax is recognized on exploratory thoracocentesis or on post mortem examination

Pulmonary infiltration is not as uncommon as one would be inclined to believe Falconer and Leonard reported hilar node involvement with direct invasion of the lung tissue in 41 7 per cent of their patients with lymphogenous leukemia Hilar lymph node involvement with intra bronchial or peribronchial spread was noted in 8 3 per cent, more or less lobar infiltration with various grades of broncho-mediastinal involvement was seen in 16 6 per cent, confluent lobular foci with associated involvement of the lymph nodes in 16 6 per cent and miliary nodulation

with widespread distribution in 16.6 per cent. The *incidence of pleuro-pulmonary involvement* was much lower in a group of 61 leukemic children studied by Falkenstein and Fowler. Pulmonary infiltration was encountered in 8 per cent and *pleural effusion in 6.5 per cent*. According to Kirshbaum and Preuss pulmonary infiltration was seen in 13 per cent of 123 cases with leukemia. The infiltration of the lung tissue with *lymphoblasts and lymphocytes is either interstitial, parenchymal or both*. Perivascular lesions are common. In addition to these specific changes it is known that pulmonary embolism or thrombosis may occur any time *during the course of lymphogenous leukemia*. *Atelectasis as well as interference* with the physiologic self cleansing capacity of the lower respiratory tract favor the invasion of the lung by pathogenic micro-organisms. Tuberculosis as a *terminal complication* has been *observed for* a long time. Pleural effusion was found in 64 per cent of the cases of Falconer and Leonard, nearly one third of these being bilateral. Also, pleural involvement, which often develops early in the disease, may result in fibrosis. These authors expressed the view that there were instances of lymphogenous leukemia with primary pleural involvement.

Lymphogenous leukemia has a biphasic predilection as to age, that is, it is the most frequent type of leukemia under 20 and over 70 years of age. Essentially, it is a neoplastic disease of the lymphoblastic portion of the hemopoietic system. It is one of the lymphomatoid diseases which may make its appearance as an independent clinical entity or in connection with *multiple follicular lymphoma, lymphosarcoma, Hodgkin's disease* and reticulum cell sarcoma. It has been proposed to distinguish three types of lymphogenous leukemia on the basis of dominant *cells in the blood*: 1) *lymphocytic*, 2) *lymphoblastic*, and 3) *lympho-sarcoma cell type*. The latter represented 36.8 per cent of 190 cases of lymphogenous leukemia studied by Bethel. Lymphocytic leukemia is encountered in middle and advanced ages. Men are more often affected by it than women. Lymphoblastic leukemia occurs exclusively during childhood, the incidence is twice as high in boys as in girls. *Lymphosarcoma* cell leukemia occurs at any age, more often in the male than in female.

Symptoms referable to the chest are cough, pain and dyspnea. Cough is provoked either by pressure of mediastinal masses of lymph nodes by pulmonary infiltration or by pleural involvement. The cough is unproductive, *rasping* and particularly distressing in the recumbent position. Pulmonary hemorrhage which is presumably due to thrombocyto-

penia occurs in less than 10 per cent of the cases It is more frequent in the acute forms Dyspnea is attributable either to mediastinal masses, pulmonary infiltration or large pleural effusion Occasionally, it may be caused by splenic hemorrhage Naturally, respiratory symptoms are increased with the onset of pulmonary complications, such as bronchopneumonia or tuberculosis and also, with the development of heart failure with pulmonary congestion and edema

Great variations are noted in the symptoms of lymphogenous leukemia in general Usually, there is a progressive, painless enlargement of the cervical, axillary and inguinal lymph nodes Nausea, vomiting and abdominal pain may be complained of The latter may be localized in the gastric region or the flank and is most likely due to splenomegaly Subcutaneous hemorrhages following slight trauma may be observed by the patient for years before he seeks medical attention Other symptoms referable to the skin are pruritus, excessive sweating, erythema and papulomacular urticaria Headache is not infrequent Pains in the bones, joints and soft tissues of the extremities are common Severe bleeding may follow a trivial surgical intervention or tooth extraction Soreness in and bleeding from the gum are frequent complaints Hemorrhages from other sites are also encountered These include nose bleed, hematemesis, melena, hematuria, menorrhagia, conjunctival, retinal and cerebral hemorrhages. Thrombocytopenia is the most likely cause of the hemorrhagic tendency The incidence of priapism varies from 0 5 to 25 per cent Superior vena caval syndrome may supervene with edema congestion and cyanosis of the soft tissues of the upper chest, neck and face, engorgement and distention of the blood vessels in the same area protrusion of the eye balls, congestion of the nasal and oropharyngeal mucous membrane Dizziness, visual disturbances and impaired hearing are occasional complaints Leukemic involvement of the central nervous system and severe anemia may be responsible for these manifestations Anemia and fever are the most frequent symptoms These, together with the increased metabolic rate explain the patient's pallor, weakness lassitude, palpitation and insomnia The basal metabolic rate may be as high as +40 or +50

Diagnosis

Roentgenologic examination of the chest may reveal mediastinal masses, enlarged hilar lymph nodes together with an accentuation of the bronchovascular markings, opacities which represent segmental or lobar infiltration, or widespread miliary nodulation Complications, such

as atelectasis, bronchopneumonia and tuberculosis are suspected from well known changes associated with these conditions Angiocardiography is a safe and valuable method for the demonstration of mediastinal vascular occlusion

Physical findings over the chest correspond to the type and extent of the mediastino pulmonary involvement There may be dull percussion note over *the manubrium of the sternum and certain areas of the* lung Rales are absent unless there is a partial occlusion of one of the major bronchi or superimposed pulmonary infection Rarely, bronchial compression by enlarged lymph nodes causes localized emphysema on one side (check valve effect) Tenderness may be found on percussion of the sternum Large pleural effusion causes distention of the respective hemithorax with respiratory lag Exploratory thoracocentesis shows clear serofibrinous fluid or chylothorax in such cases

The only conclusive method for establishing the diagnosis is the examination of the peripheral blood or, preferably, of aspirated bone marrow The essential characteristic of this disease is the appearance of large number of immature white blood cells with a total leucocyte count over 10 000 per cubic millimeter The latter may reach 200 000 or 500 000 or rarely over 1 000 000 It is axiomatic that it is not so much the number of the white blood cells as their qualitative changes that are a prerequisite of correct diagnosis *In a number of instances typical* immature white blood cells are seen with a normal or low leucocyte count Such instances are classified as aleukemic or subleukemic leukemias and represent a specific group of this disease Two points are worthy of remembering in this connection 1) Shift from a subleukemic to a high leucocyte count and vice versa is known to occur 2) Low white blood cell count with otherwise characteristic manifestations of leukemia may be found in very early and in terminal cases of this disease Pulmonary infiltration has been observed in subleukemic leukemia In Wiseman s case, roentgenogram of the chest revealed bilateral enlarged hilar shadows bronchopneumonia like shadows in the right lung together with fine small scattered infiltrations in both lungs Five months previously only enlargement of the hilar lymph nodes was noted on the x ray film The number of thrombocytes is decreased both in acute and in chronic lymphogenous leukemia Severe hypochromic anemia is frequent *For the sake of accurate* diagnosis and competent follow up it is mandatory to do repeated blood counts and/or examinations of the bone marrow

General physical examination may show [illegible] following findings 1) Enlargement of the cervical, axillary and inguinal lymph nodes It should be kept in mind however that there are instances of lymphogenous leukemia without abnormal [illegible] groups 2) The spleen is less often enlarged th[illegible] leukemia but sometimes splenomegaly is the only [illegible] rule the enlargement of the liver is not as great a[illegible] kemia 4) Examination of the oral mucosa may sh[illegible] 5) Purpura and maculopapular urticaria ma[illegible] be seen [illegible] of the skin 6) The characteristic manifestations of [illegible] obstruction have been mentioned previous[illegible] extremities may be noted even in the absence of [illegible] tion It is caused by enlarged inguinal lymph [illegible] the flow of lymph

With reference to differential diagnosis [illegible] symptoms and signs should be excluded. The[illegible] berculosis and other pulmonary infections [illegible] sitic or virus) benign and malignant neopla[illegible] stinum subacute bacterial endocarditis genera[illegible] matic fever Gaucher s disease Banti s disease [illegible] tic anemia thrombocytopenic purpura infec[illegible] Vincent s angina For the differentiation of [illegible] genograms the reader is referred to the chapte[illegible] the Lung

Myelogenous Leukemia

Myelogenous leukemia is most frequent [illegible] clusive of the sixth decade It is a neoplastic d[illegible] system with decrease in the bone marrow and w[illegible] in the liver and spleen On hematologic examina[illegible] high percentage of myelocytes and myeloblasts The [illegible] bocytes is normal or increased Viscosity of the blood [illegible] is moderate or marked anemia X ray changes in the [illegible] and occur only late in the disease Pulmonary infiltra[illegible] in various forms similar to that seen in lymphogen[illegible] addition to the aforementioned pathologic changes [illegible] have also been described which measure from 2 to 5 [illegible] Joachim and Loewe noted transitory pulmonary in[illegible] with chronic myelogenous leukemia Consolidati[illegible] in a ca[illegible] logically demonstrable pulmonary cavitation in the [illegible] upper lobe

was observed by Dubois Ferriere Symptoms of this condition are similar to those of *lymphogenous leukemia* The diagnostic approach is the same in the two conditions When pulmonary *infiltration is present* x ray films of the chest show either segmental or lobar *consolidation or* widely scattered miliary nodulation When hydrothorax develops as a complication, the pleural effusion is either serofibrinous, chylous or sanguineous There may be pain in the bones on pressure Schultz recorded the occurrence of positive heterophile antibody or Paul Bunnell test with titers which are diagnostic, that is, 1 56 or over Concerning differential diagnosis, it is well to bear in mind that there are a number of diseases with leukemoid changes These include, according to Heck and Hall, 1) acute pyogenic infections or exacerbation of chronic infections, 2) nonpyogenic infections, such as tuberculosis and whooping cough, 3) hemolytic anemia, 4) pernicious anemia, 5) polycythemia vera, 6) essential thrombocytopenia, 7) any severe anemia, 8) tumors with mestatases to bones, 9) multiple myeloma, 10) osteosclerosis and Albers Schoemberg disease, 11) diabetic coma, and 12) chemical poisoning In any of these conditions immature products of the myelogenous system may be found in the peripheral blood

For completeness sake, mention should be made of two other forms of leukemia, namely, the so called monocytic type and the stem cell type They still occupy a somewhat doubtful place in hematology as separate clinical entities Their clinical manifestations are the same as those of lymphogenous and myelogenous leukemias

Acute leukemia is far more common in children than in adults Boys are more often affected than girls Predilection as to sex is less pronounced in young children It is a severe disease associated with fever, headache, prostrations, aches and pains in the bones and joints, bleeding sore gums, petechiae, mucosal hemorrhages, vomiting and diarrhea Enlargement of the cervical lymph nodes is frequent Extensive lymph node enlargement is suggestive of lymphogenous leukemia Hepatomegaly and splenomegaly may be present Superior vena caval syndrome may result from massive enlargement of the mediastinal lymph nodes Grave anemia and hemorrhages from various sites are common Pulmonary consolidation has been observed in acute leukemia

The differentiation of immature myeloid and lymphoid blood cells is often very difficult in acute leukemia Thus the classification of the latter is often problematical In acute myelogenous leukemia the oxidase

test and indophenol synthesis test of the blood are positive in contrast to lymphogenous leukemia

Prognosis

All types of leukemias are inevitably fatal Even so, there are differences between the various forms of this disease, with reference to its course Acute leukemia has the gravest prognosis, regardless of the age of the patient It terminates in death in from few days to several weeks Spontaneous remission occurs in chronic lymphogenous leukemia but it is rare in chronic myelogenous leukemia The average duration of life in lymphogenous leukemia is three and one half years after the onset of symptoms Data presented by Bethell closely parallel general clinical experience He found the following life expectancy in the different categories of lymphogenous leukemia lymphoblastic cell type, four months, lymphosarcoma cell type, 31 3 months, and lymphocytic leukemia 58 2 months The average duration of life in myelogenous leukemia is about the same as in lymphogenous leukemia The prognosis is not dependent on or correlated to the level of white blood cell count To quote Haden leukemia may be just as malignant with 2 000 as with 200,000 cells per cubic millimeter of blood Abnormally low thrombocyte count always implies grave prognosis The cause of death may be some complicating infection, such as pneumonia, tuberculosis, some form of severe hemorrhage or cerebral embolism

Treatment

In spite of the invariably fatal prognosis of leukemias no effort should be spared in attempting to alleviate the patient s symptoms and to restore him to a reasonable measure of comfort Although the cure of this disease is still beyond the reach of clinical medicine we have efficacious methods of treatment at our disposal Unfortunately, none of the methods to be presented is applicable to the treatment of acute leukemia, except those considered purely symptomatic and supportive

Fowler s solution (solution of potassium arsenite) was first used for the treatment of myelogenous leukemia by Lissauer in 1865 It is a 1 per cent watery solution of arsenic trioxide It has no value in the treatment of lymphatic leukemia But, its therapeutic influence has been proved beyond the shadow of a doubt in the management of myelogenous leukemia, despite an avalanche of adverse criticism The medical profession owes much gratitude to Forkner for his incessant championing this drug and for its reintroduction in the management of this dis

ease His extensive clinical studies prove that benefits derived from the use of Fowler's solution are comparable to those of treatment with radium or x ray[f] Remissions can be achieved with regularity by the administration of this drug Not only the leucocyte count can be reduced to normal but also the metabolic rate, the size of the enlarged liver and spleen The patient gains in weight and attains a sense of general well being

It is well to observe a precise schedule of administration of Fowler's solution, as has been done for decades by continental clinicians The initial dose is from 3 to 4 minims (0 2 — 0 3 cc) three times a day immediately after meals, well diluted in fruit juices or coffee The dose is increased by one minim daily until from 8 to 15 minims are given three times a day It is mandatory to adjust the dose to the patient s condition, with due attention to symptoms, signs and hematologic findings Forkner s summary of commentaries is worth quoting "Along about the tenth or twelfth day the leucocyte count begins to drop precipitously Within a few days the patient begins to feel better, the anemia is lessened and all the symptoms of remission become apparent As soon as the leucocyte count reaches normal or near normal, the dose is gradually decreased by about the same rate of one minim (0 06 cc) a day until the patient is taking four or five minims three times a day and with that dose he can be maintained for many months, during which the remission will persist Patients who respond well to arsenic respond well to irradiation Occasionally, a patient will respond to arsenic who will not respond to irradiation and vice versa, but that is not the rule

X ray irradiation was first used for the treatment of leukemia by Pusey in 1902 and Senn in 1903 Since then a great deal of precision has been attained in the application of this treatment There are three methods in use 1) Heublein s method which resorts to the irradiation of the whole body with an average daily dose of 20 r (roentgen units) from a distance of from 15 to 20 feet (4 5 6 meters) for a total dose of from 200 to 400 r during a two week period If special circumstances require, the total dosage may be increased to 1,200 r in several weeks (One r is the quantity of x ray or gamma ray radiation the corpuscular emission of which per 0 001293 gram of air produces, in air, ion carrying one e s u of quantity electricity of either sign) 2) Spray technique consists of a high voltage irradiation of the entire body from a distance of from 20 to 40 inches (50 — 100 cm) with a total dose of from 50 to 60 r given in a few minutes 3) Local irradiation to the spleen and

enlarged lymph nodes in lymphogenous leukemia, to the spleen and bones in myelogenous leukemia Dowdy and Lawrence emphasized the advantages of using small dosage They advise from 25 to 50 r for the initial treatment This may be increased gradually to 75 r a day For patients with subleukemic leukemia, they recommend 50 r as the highest single dose for consecutive daily treatments. The technical factors are 200 kilovolt 25 milliampere, 50 cm distance, portal 10 by 15 or 15 by 15, filter 0.5 mm copper and 1 mm aluminum Craver saw favorable results in chronic myelogenous leukemia with splenomegaly from irradiation of the spleen three to four times with 100 r anteriorly and posteriorly The technical factors were 250 kilovolt, 70 cm distance, filter 1 5 mm copper In case of generalized manifestations of chronic lymphogenous leukemia he recommends the administration of from 200 to 300 r once around to each diseased area Bethell (1943) reports favorable results from irradiation with from 100 to 200 r to each area of involvement, taking one field on consecutive days He recorded from good to excellent therapeutic response in nearly 90 per cent of cases with chronic myelocytic leukemia Good or very good results were seen in 41 2 per cent of myelomonocytic leukemia cases His experience was disappointing in chronic myeloblastic form of the disease But, from good to excellent therapeutic response was observed in 84 per cent of patients with chronic lymphocytic leukemia

In connection with the x ray treatment of these patients, the following points deserve special attention

1 Indication for x ray irradiation should be based on a composite assaying of the patient including symptoms physical, x ray and hematologic findings. The same careful evaluation of these factors is required for the administration of repeated courses of treatment

2 Patients with acute leukemia or in the terminal stage of the disease are not to be treated with x ray irradiation

3 Some individuals show unexplainable refractoriness to this treatment Early recognition of this fact calls for some other form of specific therapy

4 Severe depression of the hemopoietic system may ensue after relatively small doses of x ray radiation particularly in children

5 X ray treatment is not contraindicated in subleukemic forms of this disease provided the patient is not in the terminal stage

6 There are instances in which subleukemic status is changed into a leukemic one under the influence of x ray irradiation

ease His extensive clinical studies prove that benefits derived from the use of Fowler's solution are comparable to those of treatment with radium or x ray[1] Remissions can be achieved with regularity by the administration of this drug Not only the leucocyte count can be reduced to normal but also the metabolic rate, the size of the enlarged liver and spleen The patient gains in weight and attains a sense of general well being

It is well to observe a precise schedule of administration of Fowler's solution, as has been done for decades by continental clinicians The initial dose is from 3 to 4 minims (0 2 — 0 3 cc) three times a day immediately after meals, well diluted in fruit juices or coffee The dose is increased by one minim daily until from 8 to 15 minims are given three times a day It is mandatory to adjust the dose to the patient's condition, with due attention to symptoms, signs and hematologic findings Forkner's summary of commentaries is worth quoting "Along about the tenth or twelfth day the leucocyte count begins to drop precipitously Within a few days the patient begins to feel better, the anemia is lessened and all the symptoms of remission become apparent As soon as the leucocyte count reaches normal or near normal, the dose is gradually decreased by about the same rate of one minim (0 06 cc) a day until the patient is taking four or five minims three times a day and with that dose he can be maintained for many months, during which the remission will persist Patients who respond well to arsenic respond well to irradiation Occasionally, a patient will respond to arsenic who will not respond to irradiation and vice versa, but that is not the rule'

X-ray irradiation was first used for the treatment of leukemia by Pusey in 1902 and Senn in 1903 Since then, a great deal of precision has been attained in the application of this treatment There are three methods in use 1) Heublein's method which resorts to the irradiation of the whole body with an average daily dose of 20 r (roentgen units) from a distance of from 15 to 20 feet (4 5 6 meters) for a total dose of from 200 to 400 r during a two week period If special circumstances require, the total dosage may be increased to 1,200 r in several weeks (One r is the quantity of x ray or gamma ray radiation, the corpuscular emission of which per 0 001293 gram of air produces, in air, ion carrying one e s u of quantity electricity of either sign) 2) Spray technique consists of a high voltage irradiation of the entire body from a distance of from 20 to 40 inches (50 — 100 cm) with a total dose of from 50 to 60 r given in a few minutes 3) Local irradiation to the spleen and

enlarged lymph nodes in lymphogenous leukemia to the spleen and bones in myelogenous leukemia Dowdy and Lawrence emphasized the advantages of using small dosage They advise from 25 to 50 r for the initial treatment This may be increased gradually to 75 r a day For patients with subleukemic leukemia, they recommend 50 r as the highest single dose for consecutive daily treatments The technical factors are 200 kilovolt 25 millampere, 50 cm distance, portal 10 by 15 or 15 by 15 filter 0.5 mm copper and 1 mm aluminum Craver saw favorable results in chronic myelogenous leukemia with splenomegaly from irradiation of the spleen three to four times with 100 r anteriorly and posteriorly The technical factors were 250 kilovolt, 70 cm distance, filter 1.5 mm copper In case of generalized manifestations of chronic lymphogenous leukemia he recommends the administration of from 200 to 300 r once around to each diseased area Bethell (1943) reports favorable results from irradiation with from 100 to 200 r to each area of involvement taking one field on consecutive days He recorded from good to excellent therapeutic response in nearly 90 per cent of cases with chronic myelocytic leukemia Good or very good results were seen in 41 2 per cent of myelomonocytic leukemia cases His experience was disappointing in chronic myeloblastic form of the disease But from good to excellent therapeutic response was observed in 84 per cent of patients with chronic lymphocytic leukemia

In connection with the x ray treatment of these patients, the following points deserve special attention

1 Indication for x ray irradiation should be based on a composite assaying of the patient including symptoms physical x ray and hematologic findings. The same careful evaluation of these factors is required for the administration of repeated courses of treatment

2 Patients with acute leukemia or in the terminal stage of the disease are not to be treated with x ray irradiation

3 Some individuals show unexplainable refractoriness to this treatment Early recognition of this fact calls for some other form of specific therapy

4 Severe depression of the hemopoietic system may ensue after relatively small doses of x ray radiation particularly in children

5 X ray treatment is not contraindicated in subleukemic forms of this disease provided the patient is not in the terminal stage

6 There are instances in which subleukemic status is changed into a leukemic one under the influence of x ray irradiation

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It is well to observe a precise schedule of administration of Fowler s solution, as has been done for decades by continental clinicians The initial dose is from *3* to 4 minims (0 2 — 0 3 cc) three times a day immediately after meals, well diluted in fruit juices or coffee The dose is increased by one minim daily until from *8* to *15* minims are given three times a day It is mandatory to adjust the dose to the patient s condition *with due attention to symptoms, signs and hematologic findings* Forkner s summary of commentaries is worth quoting Along about the tenth or twelfth day the leucocyte count begins to drop precipitously Within a few days the patient begins to feel better, the anemia is lessened and all the symptoms of remission become apparent As soon as the leucocyte count reaches normal or near normal the dose is gradually decreased by about the same rate of one minim (0 06 cc) a day until the patient is taking four or five minims three times a day and with that dose he can be maintained for many months during which the remission will persist Patients who respond well to arsenic respond well to irradiation Occasionally, a patient will respond to arsenic who will not respond to irradiation and vice versa, but that is not the rule

X ray irradiation was first used for the treatment of leukemia by Pusey in *1902* and Senn in *1903* Since then, a great deal of precision has been attained in the application of this treatment There are three methods in use. 1) Heublein's method which resorts to the irradiation of the whole body with an average daily dose of 20 r (roentgen units) from a distance of from 15 to 20 feet (4 5 6 meters) for a total dose of from 200 to 400 r during a two week period If special circumstances require the total dosage may be increased to 1 200 r in several weeks (One r is the quantity of x ray or gamma ray radiation the corpuscular emission of which per 0 001293 gram of air produces, in air, ion carrying one e s u of quantity electricity of either sign) 2) Spray *technique* consists of a high voltage irradiation of the entire body from a distance of from 20 to 40 inches *(50 — 100 cm) with a total dose of from 50* to 60 r given in a few minutes 3) Local irradiation to the spleen and

the administration desoxycorticosterone acetate which is a synthetic hormone of the suprarenal gland

Beeler and his collaborators used dramamine (beta-dimethylaminoethyl benzohydryl ether 8-chlorotheophyllinate) successfully in the treatment of radiation sickness They gave 100 mg of the drug from 30 to 60 minutes before treatment and one and one half and three hours after treatment In some cases a total dose of 200 mg was sufficient, while others required 400 mg Side effects, such as drowsiness, "bad taste," paresthesias and nausea were noted in a small percentage of patients Dramamine may be used prophylactically For severe cases, they recommended the combined administration of dramamine and pyridoxine hydrochloride (vitamin B_6)

8 Utmost care should be exercised so as to avoid overtreatment

Radium treatment is known to be useful in certain forms of chronic myelogenous leukemia According to Desjardins and Williams, satisfactory remissions can be attained by the topical application of radium over the enlarged spleen

Benzene (benzol) was first used by Koranyi in 1912 for the treatment of leukemia Recent careful clinical investigations have vindicated the efficacy of this drug when given in doses of 4 Gm (60 grains) daily in capsules, orally with olive oil It is interesting to meditate on how through the caprices and inconsistencies of medical reasoning, idle conservatism or unmotivated prejudice, benzene as a drug for the treatment of leukemia has fallen into virtual discard during the past decades

Radioactive phosphorus (radio phosphorus, phosphorus isotope, P^{32}) was introduced by Lawrence and his associates in 1939 in the treatment of myelogenous leukemia Its therapeutic action is due to its destructive effect on cells and on its greater affinity to hemopoietic tissues which have a higher metabolic rate than other tissues Its preparation is carried out as follows In a cyclotrone, ordinary red phosphorus with an atomic weight of 31 is bombarded with deutrons, electric nuclei of heavy hydrogen Consequently, an additional neutron enters the atomic structure of phosphorus Thus, the latter becomes heavier, its atomic weight being 32 Now it consists of 15 protons and 17 neutrons instead of the usual 15 protons and 16 neutrons This new electro-structural combination is unstable, for the newly added neutron has a tendency to change into a proton This change forces the discharge of one electron from the atom The electron discharged is nothing but beta ray The latter is highly radioactive. Radioactive phosphorus has an emission of

7 Radiation sickness is common in patients subjected to x ray therapy In spite of exhaustive efforts, the mechanics of the development of this condition is not known Its symptoms are anorexia, nausea vomiting, *diarrhea, tenesmus, malaise, headache, dizziness, palpitation* nervous irritability, insomnia and occasional fever These symptoms may be associated with tachycardia, arrhythmia, fall in blood pressure increased sedimentation rate of the erythrocytes, leukopenia *and thrombocytopenia* For its prevention and treatment, proper physical conditioning *of the* patient is of value His general nutritional status should be improved and, if possible, brought up to par The fluid and salt intake *should be increased Inasmuch as psychogenic factors may have some* role in the causation of roentgen sickness, it is well to handle the patient with proper care in this respect Sedative doses of the barbiturates or their equivalent may be helpful Drugs which have been advocated for the treatment of this condition include calcium thiamine chloride liver extract, vitamin B complex, intestinal antispasmodics and antihistaminic compounds Pyridoxine hydrochloride (vitamin B_6) is likely to bring about satisfactory relief It can be given orally in doses of 50 mg four hours before treatment, followed by 25 mg twice a day Also it is *administered intravenously in doses of 50 to 200 mg* before irradiation or when symptoms develop Also satisfactory results have been observed from the administration of *niacin (vitamin B_5) in doses of 200 mg* (3 grains) three times a day Forkner recommends a diet low in proteins and high in carbohydrates for a few days before and a week after x ray treatment His reasoning was in offering this diet to prevent overwhelming the body by metabolites of protein Destruction of tissue proteins during x ray irradiation is a potent source of the latter Weichert successfully treated radiation sickness with adrenal cortical hormone The [illegible]

cortical hormone counteracts mineral losses caused by sup[illegible] sufficiency 2) It has an important role in the inactivation of histamine 3) It protects *the liver against radiation induced fatty* changes 4) It lessens damage of the bone marrow 5) It prevents exhaustion of the cortex of the *suprarenal gland which is brought about by histamine-like* substances produced by x ray irradiation through stimulation of the anterior pituitary The latter produces an oversupply of corticotropic hormone which results in exhaustion of the suprarenal gland Ellinger was able to relieve radiation sickness in 74 per cent of the cases with

therapeutic response is decrease in the number of white blood cells and an increase in the number of red blood cells It is advisable to check the patient on weekly visits during treatment so as to ascertain symptoms, physical and hematologic findings

In their authoritative work, Erf and his collaborators (1941) report on their experience with radioactive phosphorus which was given in doses of from 1 to 20 millicuries depending upon the age of the patient and the type of the disease There was no improvement in patients with acute myelogenous leukemia Of patients with acute lymphatic leukemia, partial remission was noted in 16 per cent and complete remission in 16 per cent Chronic myelogenous leukemia responded with partial remission in 28 per cent and with complete remission in 13 per cent The corresponding figures were in chronic lymphogenous leukemia 32 per cent and 4 per cent, respectively

Reinhard and his associates found no improvement from the use of radioactive phosphorus in acute leukemia In chronic myelogenous leukemia, 10 per cent of the patients had fairly complete recovery Some of their patients were followed for more than three years Remissions may last for more than one year without further treatment They observed reduction in the size of the spleen in three fourths of their cases The previously enlarged spleen was not palpable at the completion of the treatment in one third of the cases No benefits were noted in monocytic leukemia Results in lymphogenous leukemia were comparable to those obtained by x ray therapy

Radioactive sodium was first investigated by Hamilton in 1937, 1942 and Hamilton and Stone in 1937 as a means for treating leukemia Its therapeutic value was assayed by Thygesen and his collaborators The salient therapeutic features of this drug as well as pertinent clinical experience with it have been summarized in the report of Evans and his associates Compared with x ray therapy treatment with radioactive sodium (Na^{24}) is advantageous, for its radiation energy includes the entire body, with maximum influence on the blood and other body fluids Its gamma ray component exerts a general irradiation, while a more localized radiation effect upon the blood is derived from the beta ray component Sodium isotope (Na^{24}) appears to be superior to radioactive phosphorus for the following reasons 1) The radiation potency of a single dose of radioactive sodium is much shorter than that of P^{32} namely, a half life of 14 8 hours against 14 3 days In view of this, the administration of the former is easier both with regard to frequency

37 million beta particles per second This represents a radiation of one millicurie In association with the discharge of beta rays from P^{32} a new balance takes place within its atomic structure in that there will be 16 neutrons, 16 protons and 16 electrons In this manner P^{32} is transformed into sulfur Half of the mass of P^{32} is changed into sulfur in 14 3 days and therefore only half as many electrons are discharged at this time as at the start This time factor is referred to as the *half life* of radioactive phosphorus Lately, Lawrence and his collaborators produced P^{32} by subjecting ordinary sulfur to neutron bombardment

For the *purpose of therapeutic administration radioactive phosphorus* is converted into dibasic sodium phosphate (Na_2HPO_4) Its standard solution contains from 15 to 18 mg of the drug per cubic centimeter of water It is made isotonic with sodium chloride and has a pH 7 4 Freshly prepared solution of radioactive sodium phosphate contains from 0 2 to 0 4 millicuries per cubic centimeter (One millicurie represent one-one thousandth of the radiation energy of one gram of radium) This freshly prepared solution is mixed with equal parts of orange juice and is taken before breakfast From 25 to 50 per cent of the radioactive phosphorus is excreted in the urine and feces during the first six days only 15 per cent of the original dose remaining in the body at the end of two weeks It completely disappears in six to eight weeks Retention of the drug in the body is less after oral than intravenous administration Diarrhea interferes with absorption of the orally administered drug

Lawrence and his associates prescribe from 1 to 2 millicuries of radioactive phosphorus once or twice a week for four to eight weeks The course is being repeated with recurrence of signs and symptoms of leukemia Some of their patients were given as much as 40 millicuries intravenously over a period of 72 days others, 70 millicuries of the drug orally over a period of 90 days Of their 129 patients treated with radioactive phosphorus 25 per cent lived five or more years after the onset of symptoms Of these, two patients were alive in reasonable physical comfort after nine or more years. Susceptibility and therapeutic response of patients to this treatment is variable In some patients 5 millicuries given in one or two doses may be as effective or may cause over effect in leukopenia and platelet depression as 30 millicuries given in several weeks to other patients. Local x ray irradiation of the spleen may be combined with the simultaneous intravenous administration of small doses of phosphorus isotope Bone marrow specimens are examined before and at the end of treatment or more often if necessary The usual

therapeutic response is decrease in the number of white blood cells and an increase in the number of red blood cells. It is advisable to check the patient on weekly visits during treatment so as to ascertain symptoms, physical and hematologic findings.

In their authoritative work, Erf and his collaborators (1941) report on their experience with radioactive phosphorus which was given in doses of from 1 to 20 millicuries depending upon the age of the patient and the type of the disease. There was no improvement in patients with acute myelogenous leukemia. Of patients with acute lymphatic leukemia, partial remission was noted in 16 per cent and complete remission in 16 per cent. Chronic myelogenous leukemia responded with partial remission in 28 per cent and with complete remission in 13 per cent. The corresponding figures were in chronic lymphogenous leukemia 32 per cent and 4 per cent, respectively.

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of treatments and the adjustment of dosage according to individual requirements. 2) The excretion of radioactive sodium *is not as great* and variable as that of radioactive phosphorus. 3) By the oral administration of *radioactive sodium* one can avoid the complications and limitations of intravenous injections of radioactive phosphorus.

Radioactive sodium is administered by mouth in the form of a less than one per cent solution of sodium chloride well diluted in two or three small lots, 10 to 15 minutes apart, followed by an equal amount of water so as to rinse the mouth. Evans and his collaborators recommend that the initial dose should be less than 0.18 millicuries per kilogram of body weight and that subsequent doses should be adjusted to the individual requirements and sensitivity of the patient. In chronic lymphogenous and myelogenous leukemia satisfactory reduction in symptoms is attainable with from 12 to 30 treatments over a period of 300 to 900 days with a total dosage of 200 to 575 millicuries. They state that the rate of response to each treatment appears to be intermediate between that of x ray irradiation and treatment with radioactive phosphorus.

Nitrogen mustards have been found useful in the treatment of certain types of leukemias. Pertinent data relative to their chemistry, dose and mode of action are presented in the chapter on Lymphomatoid Diseases of the Chest. Jacobson and his associates observed significant remissions from their use in chronic lymphogenous leukemia. Remissions lasted from 2 to 21 months. A substantial percentage of patients with chronic myelogenous leukemia showed satisfactory improvement on this treatment with remissions of 6 to 12 months duration. Goodman *et al* recorded some measure of hematologic and clinical improvement in 40 per cent of patients with acute and subacute leukemia. In chronic myelogenous leukemia about the same degree of symptomatic and hematologic improvement was achieved with nitrogen mustards as with x ray irradiation. Wintrobe and his associates used a nitrogen mustard known as HN2 or the hydrochloride salt of di (beta chloroethyl) methyl amine the chemical formula of which is $CH_3N(C_2H_4Cl)_2$. They recorded restoration of the leucocyte count and the number of thrombocytes to normal together with correction of anemia by this treatment in chronic myelogenous leukemia. Simultaneously, the spleen greatly decreased in size. Also gain in weight and a sense of well being were noted. In some cases, treatment every two to six weeks with two to three injections on successive days was adequate to give the patient satisfactory physical comfort. They observed only slight or no response to this treatment in

patients with long standing lymphogenous leukemia with marked enlargement of the lymph nodes and the spleen and with severe thrombocytopenia and anemia The summary of their observations is given in the following table

	Results		
	Good Per Cent	Fair Per Cent	Poor Per Cent
Chronic myelogenous leukemia	43	14	43
Chronic lymphogenous leukemia	30	10	60
Acute leukemia	—	38	62

SK 136 is a new nitrogen mustard derivative which is chemically 1 3 propane diamine NNN'N' tetrakis (2 chloroethyl) dihydrochloride Burchenal reports on its use in the treatment of leukemia It is given by injections in doses of 0 1 mg per kilogram of body weight daily for four to eight doses It causes less nausea and vomiting than the hydrochloride salt of di- (beta chloroethyl) methyl amine, but induces slight dizziness Satisfactory remissions were noted with this drug in chronic myelogenous leukemia comparable to that seen with the use of the aforementioned nitrogen mustard, radioactive phosphorus, or x ray therapy Some patients who do not respond to the latter measures, occasionally may improve on SK 136

Urethane (ethyl carbamate) ($C_2H_5OCONH_2$) was first used in the treatment of leukemia by Patterson and her associates in 1946 Its odorless and colorless scales or crystals have a slightly salty or bitter taste It is administered in doses of 1 Gm (15 grains) three times a day in simple syrup or in capsules with magnesium oxide Its therapeutic action is attributed to the inhibition of the mitotic cycle in hemopoiesis, although it may have some influence on the metabolism and the process of maturation of the blood cells It causes marked reduction in the number of leucocytes, decrease in the size of the spleen and correction of anemia Simultaneously, there is a noticeable improvement in the patient's general condition, with myelogenous and lymphogenous leukemia These results, however, are only temporary and do not represent curative effect No beneficial results are seen from its use in acute leukemia These investigators as well as others have pointed out that this drug has only a narrow margin of safety Overdosage may easily lead to hemopoietic aplasia and hemorrhagic tendency Also, it has been found that with repeated courses, the drug loses its efficacy, that is, the patient becomes less responsive to it This development of resistance to treatment is known to

occur with all other forms of therapy in the leukemias Hirschboeck and his fellow workers (1948) have observed satisfactory results from urethane in cases of chronic myelogenous and lymphogenous leukemia They prescribed 1 to 2 Gm (15-30 grains) of the drug three times a day given in the form of capsules *enteric coated tablets or intramuscularly* For the latter, a 50 per cent solution was used in 2 to 4 cc doses three times a day No local irritation was observed after intramuscular injec *tions but there were frequent drowsiness* and *dizziness from its hypnotic* effect Oral administration, however, may be followed by nausea and vomiting These symptoms are likely to disappear after two to three weeks of treatment Hematologic status and clinical manifestations were favorably influenced by urethane Splenomegaly was reduced malaise relieved, excessive perspiration and headache disappeared

Folic acid (pteroyl glutamic acid) antagonists such as alpha methopterin and aminopterin have caused remission in children with acute leukemia according to Farber Aminopterin is given in daily doses of 0 5 to 1 mg Toxic effects are bound to occur These include stomatitis, intestinal mucosal ulceration and pancytopenia Dameshek observed general and hematologic improvement with this drug in one third of his patients with leukemia

Treatment with adrenocorticotropic hormone (ACTH) and cortisone (*adrenal cortical steroid*) *may bring about temporary remission in* acute and chronic lymphatic leukemia

Favorable results may be anticipated in chronic myelogenous and lymphatic *leukemia with the use of triethylene melamine Dosage* of this drug is given in the Chapter on Lymphomatoid Diseases

Mettier and his co workers reported that treatment of four patients having chronic lymphatic leukemia and three with myelocytic *leukemia* were given 10 daily doses of desoxycorticosterone acetate and vitamin C without significant effects

General supportive and symptomatic measures should be resorted to *whenever the patient's condition so requires* These should cover the general management of the patient as well as means for controlling intercurrent infections to which patients with leukemia are notoriously susceptible In this respect, the early and adequate administration of penicillin, streptomycin and other antibiotics deserves special emphasis

Plasmacytoma

Plasmacytoma is a tumor usually found in the bone marrow It is *very rarely encountered* in extramedullary forms Of the latter type, less

than 150 cases have been recorded in the medical literature It occurs in adults only and its predilectional sites are the nasal cavity the naso pharynx tonsils and the larynx Also it may occur in lymph nodes thy roid intestinal wall kidneys ovaries and skin Klose reported a case of plasmacytoma of the pleura which invaded three ribs and the intercostal tissues The surgically removed neoplasm measured 11 by 7 5 by 5 cm Bross found a solitary plasmacytoma of the mediastinum on postmortem examination in a woman aged 54 years There was a fist sized encap sulated mass in the posterior mediastinal region without signs of in vasiveness There were no related symptoms during the patient s life Gordon and Walker (1944) cite Stewart who observed two instances of solitary plasmacytoma of the lung Also they describe the case of a woman aged 30 years whose x ray film of the chest revealed a round shadow in the upper lobe of the left lung The roentgenogram was taken on account of a low grade fever after abortion There were no associated complaints referable to the chest Following lobectomy the surgical specimen showed a firm rubbery encapsulated globular mass 5 cm in diameter Its cut surface was light pearly gray with many small areas of bright yellow color and irregular outl ne there were occasional inter lacing fibrous bands

Plasmacytomas consist of round oval or polygonal plasma cells which have basophilic cytoplasm and eccentric single or multiple nuclei Plasma cells arise from lymphocytes Individual cells of the tumor show slight variations in size Characteristically the chromatin in the nucleus of each cell is arranged in a cartwheel fashion that is in a circle about the nuclear membrane Other components of the tumor tissue are occasional giant cells and mitotic figures Russel bod es are seen as refractile hyaline acidoph lic globules within degenerated plasma cells

It is well to bear in mind that plasmacytomas may remain histo logically and clinically nonmalignant or for reasons unknown may as sume the attributes of malignant neoplasms

Symptoms signs physical and x ray findings of pulmonary plasma cytoma are similar to those seen in other neoplasms of the lung On account of the round shadows these tumors cast on the roentgenogram they should be differentiated from a number of conditions which are enumerated in the chapter on Pulmonary Adenomatosis

The only treatment for plasmacytoma of the lung is pulmonary resection

Polycythemia Vera

Polycythemia vera (polycythemia rubra vera, erythremia, Vaquez—Osler disease) was defined aptly by Weber as a primary neoplastic process in the erythroblastic portion of the bone marrow analogous to myelosis (myeloid leukemia) in the leukoblastic portion The disease is characterized by a consistently increased number of red blood cells above 6 000 000 per cubic millimeter, increase in the hemoglobin above 18 Gm per 100 cc and hematocrit above 50 per cent The occasional occurrence of associated leukemia has been observed The first instance of the combination of these two conditions was recorded by Turk (1904) The number of white blood cells may reach 100,000, with typical immature myeloid cells Furey observed myeloid elements in the blood in approximately 10 per cent of the cases The usual symptoms are fullness in the head headache, dizziness, precordial tightness, anoxia caused by the slow circulation of the blood due to its increased cell content, it may cause paresthesias in the extremities and intermittent claudication Neurologic complications are common Pulmonary hemorrhage may be a major presenting symptom

The diagnosis of polycythemia vera is based on hematologic and general physical findings Florid appearance and cyanosis of the face and lips are common Splenomegaly is usually present, also, the liver is commonly palpable The basal metabolic rate is elevated Examination of aspirated bone marrow may offer confirmatory evidence Manning states that in persons with values of hemoglobin, erythrocytes and hematocrit above the upper limits of normal and in whom causes of secondary erythrocytosis can be ruled out the following cellular pattern of aspirated sternal bone marrow is suggestive of polycythemia vera 1) The values of nucleated red blood cells, mainly erythroblasts are above 20 per 100 leucocytes counted 2) The number of reticulocytes is more than 2 per cent 3) The myeloid erythroid ratio is below 3 1

Pulmonary lesions may be found in the roentgenograms of the chest in these cases in transitory or permanent form Hisch described spherical well demarcated shadows in the lung fields in three patients Interestingly, the x ray manifestations disappeared in three weeks Hodes and Griffith observed roentgenologically demonstrable lesions of identical appearance but of permanent character The latter form should be differentiated from round x ray opacities cast by other diseases A list of these is given in the chapter on Pulmonary Adenomatosis In the opinion of Hodes and Griffith, these x ray changes are most likely due to perivascular hemor

rhage after thrombosis of a branch of the pulmonary vein, with stasis infarction and with consequent diapedesis of blood or rupture in the vein If subsequent resorption of the extravasated blood takes place, the round opacity rapidly disappears If it is replaced by fibrous tissue, a permanent pulmonary change results with a corresponding spherical shadow in the roentgenogram Accentuation of bronchovascular markings due to engorgement of the pulmonary vessels is a frequent finding in polycythemia vera

Newman and his associates concluded from their studies that the increased viscosity and volume of the blood cause a decrease in pulmonary expansibility with consequent diminution of the vital capacity of the lung and of the maximum breathing capacity The consequent impaired ventilation results in oxygen unsaturation of the blood, increased arterial carbon dioxide, respiratory acidosis and hypoxia

Treatment

Polycythemia vera can be effectively treated by various methods

1 Acetylphenyl hydrazine ($C_6H_5NHNHCOCH_3$) owes its efficacy to its hemolysing influence It is administered orally in gelatine capsules in doses of 0 1 Gm (1½ grains) once a day for a week or 10 days Decrease in the number of red blood cells begins in 10 days after the initial dose When this is accomplished 0 1 Gm (1½ grains) of the drug is given once every week or every two weeks for the purpose of maintaining the normal level of the red blood cells

2 Fowler's solution (one per cent watery solution of arsenic trioxide) exerts its therapeutic action directly upon the bone marrow and in this manner, retards its erythrogenic function The dosage schedule is given in details in connection with the treatment of leukemia

3 Radioactive phosphorus (P^{32}, phosphorus isotope) was first used by Lawrence in 1940 for the treatment of this disease It is administered in the same manner as in leukemia Its efficacy is attributed to the reduction of new red blood cell formation As a rule, results are not noticeable until the sixth to eighth week after the initial treatment for the drug has no influence upon circulating red blood cells Frf reported that 68 per cent of his patients showed satisfactory remissions which lasted from six months to three years The remissions were characterized by reduction of the erythrocyte count to normal, marked improvement in the objective clinical findings as well as in the patient s symptoms He recommends keeping these patients on a strict

red meat free diet, for he observed that remissions could be stoppe if red meat was given Iron or much liver had the same effect Reir hard used from 3 5 to 4 millicurie single dose of radioactive phosphoru given intravenously, for the initial treatment This was followed by second dose of 1 to 3 millicurie 90 days later and by a third dose at th same interval subsequently if necessary Remissions lasted from five to 3 months In addition to restoration of normal hematologic findings ir the peripheral blood, there was marked subjective improvement The spleen was reduced in size in all patients, in two thirds of them so much so that it was not palpable

4 Radioactive sodium was found to be effective in the treatment of polycythemia vera by Evans and his associates They used the same *dosage as given for the treatment of leukemia*

5 Nitrogen mustards are capable of inducing significant remissions in polycythemia vera according to the report of Spurr and his collaborators Its pharmacologic effect is due to its depressive action upon the erythrogenic portion of the bone marrow Dosage and technique of its administration are outlined in the chapter on Lymphomatoid Diseases of the Chest

6 X ray therapy for this disease was first applied by Vaquez in 1904 It can be given by two methods A Irradiation of the bone marrow of the sternum and long bones alternatingly and also of the spleen, using 50 r for the treatment of each site B By the so-called spray treatment irradiation of the entire body with 50 r can be given three times a week for three to six treatments Falconer combined x ray therapy with the administration of phenylhydrazine One of his patients treated in this manner remained well for eleven years

7 Special dietary regimen has been found to exert favorable influence upon the course of polycythemia vera Herzog and Kleiner noted improvement in their patients by reducing their intake of animal albumin to less than one gram daily When on such regimen the number of red blood cells returns to normal a diet is prescribed which consists of 1 pint of milk 100 Gm of cheese and 200 Gm fish daily To this three eggs and 150 Gm of veal are added twice weekly

8 Phlebotomy, when repeated about once a month, brings about symptomatic relief Damashek and Henstell recommend keeping these patients on iron deficient diet in addition to systematic phlebotomies scheduled according to the individual requirement of the case

9 Brumpt and Gujar reported on satisfactory results in 25 patients

who were given therapeutic infection with hookworm larvae (Ancylostoma duodenale) The number of larvae applied to the skin vary from 300 to 600 Reduction in the number of red blood cells is slow and safe The infection terminates by itself in five to six years or it can be stopped medicinally any time during the course of treatment

10 Rosenthal and Rosenthal were favorably impressed by the therapeutic effect of triethylene melamine, particularly in patients with polycythemia of short duration and with normal thrombocyte and white blood cell counts The drug was given orally one hour before breakfast in doses of 2 5 or 5 mg every one to three days to a total dose of 15 to 40 mg

Lawrence pointed out that with proper treatment, the life expectancy of patients with polycythemia vera is as good as that of adequately treated patients with diabetes mellitus or of those with pernicious anemia

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PULMONARY CHANGES ASSOCIATED WITH ERYTHEMA NODOSUM

By Andrew L. Banyai M.D and J Winthrop Peabody, M D

In the light of modern investigations, erythema nodosum is considered a manifestation of hypersensitiveness to a great variety of allergens Clinically, it consists of painful raised glossy bright red or purplish ovoid nodules which measure from 1 to 6 cm in diameter and are tender on pressure They are firm and elastic, appear as multiple lesions which most frequently occupy the anterior aspects of the legs but also may be seen on the anterior and medial aspects of the knee, the ankle, sole of the foot and on the anterior and posterior surfaces of the forearms rarely on buttocks and face The nodules are surrounded by moderate perifocal edema The skin changes have a self limited course They disappear in from two to four weeks but may leave brownish areas of residual pigmentation Histologically, erythema nodosum shows infiltration of the corium and subcutaneous tissue with round cells, granulation tissue cells and polymorphonuclear leucocytes with predilectional localization about blood vessels and glands Occasionally, there is evidence of fibrinous exudation and slight subcutaneous hemorrhage

There has been a great deal of vacillation of opinions concerning the origin of this condition Mackensie thought that it was due to rheumatic fever The consensus of today strongly questions this concept. Willan in 1798 first recorded the clinical association of erythema nodosum and tuberculosis The multiplicity of its possible causes is well illustrated by the following list which includes diseases associated with or followed by erythema nodosum

Upper respiratory infection (pharyngitis tonsilitis para nasal sinusitis)

Tuberculosis

Miscellaneous pulmonary diseases

Leprosy

Sarcoidosis

Infections with streptococci such as peritonsillar abscess prostatic, axillary abscesses eye infection dental infections lung abscess postoperative infections

Communicable diseases scarlet fever measles, chickenpox small pox meningococcemia

Brucellosis

Influenza
Herpes zoster
Coccidioidomycosis
Gonorrhea
Syphilis
Lymphogranuloma inguinale
Chronic ulcerative colitis
Regional ileitis
Arthralgia and polyarthritis
Hodgkin s disease and other neoplasms
Ingestion of drugs, such as bromides, iodides sulfonamides, etc

In Europe, particularly in the Scandinavian countries erythema nodosum is looked upon as a disease of tuberculous origin in the overwhelming majority of cases In the United States the disease is usually attributed to causes other than tuberculosis Hildebrand was the first to demonstrate the presence of tubercle bacilli in the blood of these patients Cibils Aguirre of Argentina isolated tubercle bacilli by culture and guinea pig inoculation from the skin lesions The findings of Hildebrand was confirmed by the French investigators, Debre, Saenz and Broca They found tubercle bacilli in the blood in 17 per cent of their cases with erythema nodosum After the injection of 10 to 15 cc. of the patients blood into guinea pigs they noted positive tuberculin reaction in the experimental animals in from 60 to 95 days This is a much longer period than that which follows inoculation with ordinary laboratory specimens containing tubercle bacilli It was interpreted by the authors as a sign of only few tubercle bacilli in the patient's blood To the same factors was attributed the relatively slow deterioration of the animals which developed tuberculosis The animals died in from five to seven months after inoculation one of them in 10 months Debre Saenz and Broca mention the fact that tubercle bacilli were recovered from the patients blood by others only in 3 to 4 per cent of the cases with erythema nodosum

We have had the opportunity to observe this condition in association with primary tuberculosis as well as with nontuberculous infections Those who assert the tuberculous origin of erythema nodosum state that it may occur not only in primary but also in the reinfection type of tuberculosis Cases have been reported where erythema nodosum developed in connection with the bronchogenous spread of an already well established pulmonary tuberculosis Also, an apparently quiescent,

recent primary tuberculosis may result in erythema nodosum In such instances, it has been considered as being due to exaggerated sensitivity of the skin to tuberculoproteins The allergic balance of the patient may be upset by endogenous disturbances (metabolic, endocrine) or by exogenous factors, such as an infection or the intracutaneous injection of tuberculin Instances are on record in which erythema nodosum developed in patients with recent tuberculous lymphadenitis and in persons with a flare up or long standing tuberculosis of lymph nodes

Regardless of the etiology of erythema nodosum, enlargement of the hilar lymph nodes, with or without pulmonary changes, is found during the active phase of the disease in from 6 to 90 per cent of cases These lymph nodes become enlarged with the onset of the skin lesion and may be associated with increase in the size of the paratracheal lymph nodes and with transient segmental atelectasis The enlarged lymph nodes recede to normal size in from one half to two and a half years They usually, but not always appear in symmetrical nodosities bilaterally and should be differentiated from similar x-ray shadows caused by neoplastic, infectious, vascular, circulatory diseases, developmental anomalies and other conditions

Simultaneously with the enlargement of the hilar and mediastinal lymph nodes or three to four months thereafter, pathologic findings are noticeable in the roentgenograms of the lung They consist of fine reticulation radiating from the hilar region toward the periphery and of widely distributed miliary opacities or round or oval shadows of 3 to 5 mm in diameter According to Kerley, these changes are brought about by lymphatic obstruction and may disappear and recur from time to time Also, he states that miliary lesions are confined to one lung when enlargement of the hilar lymph nodes is unilateral The larger opacities may be observable throughout both lungs or only in the area of one lobe or one pulmonary segment These lung findings completely disappear in from two months to two years In some instances, diffuse interstitial fibrosis remains after recovery Pleural effusion is rarely observed but it may occur either unilaterally or consecutively bilaterally in association with enlargement of the hilar lymph nodes Nodular x ray shadows seen in erythema nodosum should be differentiated from con ditions which are enumerated in the chapter on Pulmonary Manifesta tions of Collagen Disease

Symptoms

The aforementioned data illustrate that erythema nodosum is a syndrome rather than an independent disease entity Consequently, its constitutional and localizing symptoms—discounting its skin manifestations, show great variations During its prodromal phase, the patient may complain of unexplained lassitude, weakness, loss of appetite, nausea, abdominal pain, headache, generalized, fleeting aches and pains Subsequently, the temperature may rise to 102°F Fever lasts from one to ten days

Diagnosis

For the sake of correct diagnosis, it is mandatory to take roentgenograms of the chest during the acute phase of the skin eruptions If the films do not show deviations from normal, x ray pictures of the chest should be taken at three months' intervals for one year In case of tuberculous origin of the disease, one finds strongly positive skin reactions to high dilutions of tuberculin Examination of the fasting gastric contents on repeated occasions (3 to 5) by culture or guinea pig inoculation may reveal tubercle bacilli There is nothing relevant in the blood picture for it varies according to the nature of the underlying causative factors Skin testing with coccidioidin, complement fixation, agglutination tests blood cultures or biopsy of an enlarged superficial lymph node bacteriologic examination of the sputum and pleural effusion are integral parts of appropriate diagnostic approach to this problem

Prognosis

The outcome of the skin lesions is always favorable As mentioned previously, pathologic alterations in the chest are bound to disappear European clinicians reported the development of serious forms of parenchymal tuberculosis in the lung in a number of instances within six months after the clearing of the erythematous skin changes In instances where tuberculous enlargement of the hilar and mediastinal lymph nodes is associated with detectable tubercle bacilli in the fasting gastric juice it may take from six months to one year or even longer before conversion of the bacteriologic findings to negative is noted

Treatment

Treatment is predicated upon the causative pathogenic microorganisms and allergens X ray irradiation to the enlarged hilar and mediastinal lymph nodes may be of benefit in tuberculosis Kerley and

Favour and Sosman do not recommend x-ray therapy for the management of thoracic involvement

Bed rest is recommended until the fever has been abated for a week and the sedimentation rate has become normal Painful nodules on the extremities should be protected by a heat cradle supporting the bedclothes Sodium salicylate (20 grains or 1 2 Gm q i d) is advocated by Dolkart and Dey for relief of pain Pyribenzamine (50 mg t i d) is recommended to shorten the course of the disease

Cutaneous manifestations of erythema nodosum have been successfully treated with corticotropin (ACTH) and cortisone by a number of clinicians

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FIBROCYSTIC DISEASES OF THE PANCREAS WITH ASSOCIATED PULMONARY CHANGES

By ANDREW L BANYAI, M D and J WINTHROP PEABODY, M D

Although fibrocystic diseases of the pancreas was first identified by Landsteiner in 1905, only relatively recent reports have emphasized its clinical importance It is a condition encountered in infants and young children According to Anderson and Hodges, its incidence is 3 per cent in necropsied infants and children and 1 73 per thousand live [illegible] in both sexes with about equal frequency Its etiology [illegible] offered for the ex- [illegible] editary disease

Pathologic changes in the pa[illegible] anifestations of this condition On postmortem examination, one finds this organ reduced in size and weight far below normal and that it shows a lobular appearance which is due to contracting interstitial fibrosis Histologic studies reveal the following alterations

(1) The pancreatic acini are atrophic or destroyed while the islands of Langerhans remain intact

(2) The site of excretory parenchyma lost in this manner, is replaced by cysts of varying sizes The inner surface of the latter is covered with epithelium

(3) The cysts are surrounded by fibrous tissue

(4) There is occlusion of the small excretory ducts The plugged ducts are dilated In contrast, the ducts of Wirsung and Santorini are only infrequently obstructed

(5) Fibrous tissue masses replace large areas of the pancreatic parenchyma

The pathologic changes are of progressive nature and readily become irreversible That these alterations are not caused by local influences, but are the result of constitutional factors, is well borne out by the fact that in instances where aberrant pancreatic tissue is present, identical pathologic findings are noted in it Also, this view is supported by observation of similar pathologic changes in other parts of the body Thus, excretory ducts of salivary glands may be occluded The liver is often enlarged Moreover, there are limited cirrhotic areas in this organ, with intrahepatic biliary obstruction

Grave consequences follow the aforementioned pathologic changes in the pancreas There is an insufficiency in the formation and the duodenal delivery of pancreatic secretions. In other words, there develops

a pancreatic hypochylia, *marked reduction of the* enzymes produced by this organ, namely trypsin, amylase and lipase Of these the lack of trypsin is of particular significance This functional impairment exerts manifold effects upon the digestion, *nutrition, metabolism and general* welfare of the diseased child One can readily appreciate that in the absence of normal amounts of pancreatic enzymes, there is a serious interference with the absorption of essential food elements proteins, carbohydrates and fats, together with indispensible fat soluble vitamin A and D *In spite of adequate diet and apparently good appetite, these* patients show evidence of weight loss, malnutrition or emaciation Stohl and his associates pointed out that physical deterioration in these children is due to poor retention in the body and excessive loss of nitrogen in the feces They ascertained that nitrogen loss in the feces may exceed *that found in the urine in these cases Infants with fibrocystic disease* of the pancreas, when kept on normal diet, showed fat lost in feces more than five times the normal loss

Another serious consequence of pancreatic dysfunction is attributable to diminished absorption of fat soluble vitamin A on account of the *faulty absorption of fats Concurrent pathologic changes in the* liver localized cirrhosis, degeneration with replacement by fat and also, its glycogen depletion due to malnutrition contribute in no small degree to the development of vitamin A deficiency It is known that normally about 95 per cent of the body's vitamin A content is stored in the liver *Schneider and Widman called attention to the fact that* vitamin A metabolism is closely coupled with the glycogen metabolism of the liver Furthermore, pathologic alterations *in the liver are bound to impair* the functional competency of this organ in the production of vitamin A from carotene ingested in food

Vitamin A deficiency causes specific pathologic changes in the respiratory mucosa These consist of atrophy of the epithelium with associated disappearance of the *ciliary function, proliferation* of the basal cells and replacement of the original epithelium by a stratified keratinizing epithelium Postmortem examinations of experimental animals show that these changes lead to the occlusion of bronchi, formation and filling of bronchiectatic cavities with keratinized cells and atelectasis The plugs of desquamated epithelial cells act as a culture medium for pathogenic microorganisms Postmortem findings in infants dead of pulmonary manifestations of *fibrocystic disease* of the pancreas closely resemble these observations There is an involvement of the alveoli, the

alveolar duct, bronchioles and small bronchi There is metaplasia of their lining epithelium to a stratified, squamous type The walls of the bronchioles and bronchi are thick, with evidence of frequent destruction Occlusion of the smaller air passages results from accumulation of desquamated epithelial cells and mucopurulent exudate This, in turn, is followed by patchy atelectasis Other notable pathologic findings are

(1) Peribronchial infiltration with polymorphonuclear leucocytes and lymphocytes

(2) Ectasis of the small bronchi and bronchioles, with a tendency to small abscess formation, the extent of bronchiectasis is usually proportionate to the duration of pulmonary involvement

(3) Mucopurulent bronchitis with thick, tenacious exudate

(4) Superimposed bronchopneumonia, usually, but not always caused by hemolytic Staphylococcus aureus

(5) Widespread pulmonary fibrosis, peribronchial in character or replacing some of the parenchymal tissue

Peripheral patchy emphysema

Symptoms

It is beyond the purpose of this chapter to present all the clinical manifestations of fibrocystic disease of the pancreas It may be mentioned, however, that customarily, four types of this condition are distinguished

(1) Meconium ileus which is seen in very young infants

(2) Predominantly gastro-intestinal symptoms the so-called celiac syndrome (Gee Herter Fanconi)

(3) Predominantly respiratory symptoms

(4) The combination of No 2 and 3 It is our intention to present the last in some detail According to Kennedy, in about one third of these cases, gastrointestinal symptoms precede pulmonary manifestations The number of stools is increased, the child has diarrhea or steatorrhea, rarely constipation Vomiting may be present The stools are bulky, mushy, pale, foamy, oily or greasy, and of foul odor The child shows signs of general nutritional failure, weakness, wasting and possibly dwarfism Relative to the respiratory system, there is a history of "frequent colds" The usual presenting symptom is hacking unproductive cough Subsequently, it is bound to increase in intensity, become paroxysmal, accompanied by sneezing and may assume brassy or croupy

character Extensive pulmonary disease is associated with dyspnea and cyanosis

Diagnosis

General physical examination reveals a child with typical earmarks of nutritional insufficiency and signs of retarded physical development One notes the unusual leanness and lack of subcutaneous fat pads There is definite atrophy or maldevelopment of muscles at the buttocks and shoulders The abdomen is protuberant and tympanitic on percussion often, the liver is palpable Clubbing of the fingers and toes may be present

There may be limitation in the respiratory excursions of the chest associated with hyperresonant percussion note and decreased superficial cardiac dullness On auscultation, fine and medium moist rales or sonorous and sibilant rales are audible throughout both lungs Bronchiectasis localized in the bases and circumscribed bronchopneumonia are accompanied by physical findings limited to corresponding areas

Roentgenograms of the chest are indispensible for correct diagnosis Needless to say that there are great variations in roentgenologic findings predicated upon the extent and duration of the lung lesion Even so there are certain points of diagnostic significance When pulmonary infection is present, the hilar shadows are enlarged and there is an accentuation of the bronchovascular markings There are bilateral, unusually symmetrical, irregular, mottled infiltrations, in the form of light densities, localized predominantly in the perihilar region From here they extend diffusely in a fan like fashion toward the mid zone of the lung field As a rule, there is less mottling near the periphery In addition one may note irregular small areas of atelectasis Sometimes the latter may involve an entire lobe The outer zone of the lung often shows emphysema Emphysema in these instances is obstructive in origin and it is brought about by inspissated mucus or glary mucopurulent exudate In the presence of considerable obstructive emphysema, the lung becomes distended on expiration, the intercostal spaces are widened the diaphragm occupies an abnormally low position and its dome is flattened With the increasing duration of the disease, abnormal x ray findings are bound to become more manifest With the development of considerable fibrosis, heavy linear or massive shadows are noted the latter being similar to the appearance of consolidation Bronchiectasis is suspected when the roentgenogram reveals persistent, symmetrical basal mottling accentuation of the basal bronchovascular structures, segmented appear

ance of the peripheral bronchial walls which thus gives the impression of alternating telegraphic dashes and dots along the course of the bronchi and finally, honeycomb-like picture

The value of simultaneous extrapulmonary diagnostic roentgenologic findings has been recognized by a number of clinicians Neuhauser summarized them in the following points

(1) The liver shadow is frequently enlarged

(2) There are signs of retarded bone age, osteoporosis or evidence of vitamin deficiency

(3) There is an accumulation of excessive amounts of gas in the small bowel Partial ileus of the latter is suggested by the presence of fluid levels on film taken in the upright position After the administration of barium, intestinal motility usually appears hyperactive if diarrhea is a prominent feature, but in the late stages of the disease, motility is, as a rule, lessened even though a moderate degree of diarrhea may be present Steatorrhea is associated with alternating areas of spasm and dilatation causing segmentation At the same time, there is a loss of normal mucosal pattern

Dickey, who studied 10 cases stated that fibrocystic disease of the pancreas is probably the cause of four per cent of the deaths in children The disease should be suspected in young patients having steatorrhea and a chronic cough

Laboratory studies are essential in arriving at the correct diagnosis Inasmuch as steatorrhea is present in all cases, examination of dried stools shows increased amounts of lipids With the aid of duodenal intubation and aspiration, an accurate estimation can be made of the chemical composition of the pancreatic secretions In this fashion, one finds a reduction in pancreatic enzymes (trypsin, amylase, lipase), particularly in the amount of trypsin Schwachman and his associates showed that it was feasible to determine pancreatic function by the trypsin content of stools They found no trypsin in 209 of 220 stools from 50 patients with fibrocystic disease of the pancreas Determinations of vitamin A blood levels reveal values far below normal For infants, the normal vitamin A level is 28 international units per 100 cc of serum Philipsborne and his associates recommended that this procedure should be carried out before and after the administration of 0 1 cubic centimeter of percomorph oil per pound of body weight In addition to a low vitamin A curve, one finds evidence of lowered glucose tolerance

In the presence of infection of the lower respiratory tract, there are leucocytosis and an increased sedimentation rate of the erythrocytes

From the differential diagnostic point of view, one should keep in mind obstructive diseases of the larynx, laryngotracheobronchitis, bronchopneumonia, bronchial asthma, atelectasis and bronchiectasis It was duly emphasized by Anderson that every infant with bronchiectasis should be thoroughly studied for fibrocystic disease of the pancreas

Prognosis

Fibrocystic disease of the pancreas with associated pulmonary disease has a serious prognosis In a group of 28 cases observed by Kennedy 18 (64 per cent) died before the seventh year of life, most of them between the ages of two months and two years Since clearer understanding of the mechanics of the disease has been acquired and appropriate therapeutic measures have been introduced, prospects are better for improving the patient's general condition, for prolonging life and securing complete recovery

Treatment

Management of this disease is best carried out simultanously along two lines

(1) Attention to pancreatic insufficiency and to associated digestive disturbances,

(2) Treatment of the pulmonary infection The patient is put on a fat free diet with high protein and low carbohydrate intake It should be within the digestive capacity of the child Preferably, the daily caloric intake is set from 30 to 50 per cent more than that corresponding to body weight Milk may be substituted by casein hydrolyzates to advantage

With improvement in the patient's condition, small amounts of fat and increasing quantities of carbohydrates are added to the diet The administration of pancreatin is mandatory It is prescribed in the form of granules, preferably enteric coated, and is given in doses of 15 grains (1 0 Gm) three times daily, 10 minutes before feeding Another "must in the treatment is the administration of vitamin A It is given orally 25,000 units a day or intramuscularly, 100,000 units twice a week

The pulmonary disease is treated according to the well known principles Most important of these is inhalation of aerosolized penicillin Infants and young children are kept in cellophane tents, the atmosphere of which contains 2,000 units per cubic centimeter Children

over five years of age are given penicillin through a face mask, 25,000 to 50,000 units three four times a day This treatment may be combined with intramuscular administration of this drug In case the pulmonary infection is due to penicillin resistant micro-organisms, streptomycin is given either by aerosolized inhalations or intramuscularly Schwachman and his associates observed good to excellent results with the oral administration of aureomycin The effective dose varies from 20 to 30 mg per Kg of body weight Equally gratifying results were reported by Schwachman in terramycin treated patients Ayers and his co-workers employed sympathetic denervation of the pancreas by splanchnic block with procaine hydrochloride and complete splanchnicectomy on the right side in five cases with spectacular immediate results This new method of treatment is based on the concept that by denervating the diseased pancreas a reflex arc is interrupted In this manner, transmission of abnormal stimuli from the spinal cord and the diencephalon to the lung is prevented, with consequent complete disappearance of pulmonary symptoms

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ESSENTIAL PULMONARY HEMOSIDEROSIS

By ANDREW L BANYAI, M D and J WINTHROP PEABODY, M D

This disease is also known as idiopathic brown induration of the lung, idiopathic progressive brown induration of the lung and Ceelen-Gellerstedt disease The exact pathogenesis of this condition is not known Some attribute it to an inflammatory process of unknown origin Ceelen maintains that the underlying cause is an interstitial defect of the lung tissue Gellerstedt is of the opinion that it originates from structurally imperfect pulmonary capillaries Borsos Nachtnebel believes that both structural and functional defects in the lung are the responsible factors Glanzmann and Walthard refer to it as a disease resulting from heredofamilial constitutional faulty development of the lung, with deficiency of the elastic fibers Analysis of the records of cases reported, however, reveals no familial incidence of the disease

Essential pulmonary hemosiderosis is a newly recognized, rare disease observed in infants and children One of the cases reported in the literature occurred in an adult Postmortem examination reveals that the lung is hard and reddish-brown in color The hilar lymph nodes are enlarged and somewhat brownish in appearance Histologically, one finds that the alveolar walls and the capillaries are thickened with fibrosis Also, there is a hyperemia in the capillaries and fibrous thickening of the walls of the smaller arteries and veins, together with degeneration of the elastic fibers in the walls of the alveoli and small blood vessels Pilcher and Eitzen reported on the occurrence of yellowish-green filaments in the alveolar walls, extending occasionally into the alveolar space They noted similar filaments in the bronchial walls These filaments are produced by the incrustation of degenerated elastic fibers by hemosiderin liberated from extravasted red blood cells Simultaneously, so-called siderotic nodules were also observed The alveoli are filled with desquamated epithelial cells and macrophages which contain golden-brown hemosiderin The latter is the end product of the decomposition of hemoglobin It is relatively insoluble and radiopaque Usually, there is evidence of recent alveolar hemorrhages and occasionally, inflammatory changes in the alveolar walls According to Pilcher and Eitzen, the hilar lymph nodes also show the presence of hemosiderin-containing foreign body-type giant cells and pigmented filaments In the case recorded by Anspach, inflammatory necrotizing arteritis was found in addition to interstitial fibrosis with deposits of hemosiderin The pleura

may show fibrotic thickening, focal hemorrhages and areas of golden brown pigmentation due to the deposition of the hemosiderin

Symptomatology

Cough and blood streaked sputum are the usual presenting symptoms referable to the lung Cough may be occasional or persistent and intense. Dyspnea and cyanosis are attributable to the pulmonary fibrosis characteristic of this disease Both of these symptoms are recurrent, last for several days or longer and are progressive These manifestations are associated with periodically recurring anemia which occasionally is quite severe Also, one may note marked, unexplained fatigue, great muscular weakness and sometimes fever, loss of weight, loose stools, rarely with frank intestinal hemorrhage and hematemesis Abdominal pain may be referred from subpleural hemorrhage at the base of the lung as suggested by Wyllie and his associates on the basis of observations in seven cases of their own

Diagnosis

Essential pulmonary hemosiderosis has an insidious onset It should be thought of particularly in infants and children with severe, recurrent hypochromic anemia not attributable to more common diseases The anemia is brought about by loss of blood through pulmonary hemorrhages There may be a history of respiratory insufficiency since birth Symptoms and signs referable to the lung may be aggravated by measles whooping cough and influenza Physical examination of the lungs reveals no abnormal changes Evidence of hypertrophy and dilatation of the heart may be found as the result of obstruction to the pulmonary circulation by extensive fibrosis Clubbing of the fingers has been observed, also abdominal distention, hepatomegaly and splenomegaly Roentgenograms of the chest may reveal enlarged hilar shadows, diffuse haziness over both lung fields and widespread nodular shadows or coarse, widespread mottling in both lungs These shadows are cast by the conglomeration of hemosiderin containing cells and have a tendency to periodic increase and decrease in their extent and intensity, depending upon the frequency and degree of recurrent intrapulmonary hemorrhages In some instances, the x ray picture of the chest is entirely normal, or it may show enlargement of the heart and the pulmonary conus in addition to nodular shadows in the lung fields

Hematologic examination shows severe anemia The number of erythrocytes may be reduced to less than 2,000,000 per cubic millimeter and

the hemoglobin may be as low as 20 per cent of normal Wyllie and his associates pointed out that in some instances, there was a compensatory rise in the red blood cell count, which may reach normal levels, in the final stage of the disease when anoxemia is too intense There is an accelerated sedimentation rate of the red blood cells Qualitatively, one finds microcytosis, anisocytosis and poikilocytosis The number of white blood cells varies from normal to 20,000 per cubic millimeter The differential count remains normal or there is eosinophilia

Essential pulmonary hemosiderosis should be differentiated from deposition of hemosiderin in the lung resultant to mitral valve disease and from conditions with similar symptoms particularly from lesions which cast widespread nodular shadows on the roentgenogram of the chest These are listed in the chapter on *Pulmonary Manifestations of Collagen Disease*

Prognosis

Prognosis of essential pulmonary hemosiderosis is bad It seems that virtually in all cases, fatal outcome is inevitable Its course may last as long as two years

Treatment

Treatment is symptomatic and supportive

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PULMONARY MANIFESTATIONS OF RENAL DWARFISM

By ANDREW L BANYAI M D and J WINTHROP PEABODY, M D

Renal dwarfism (renal infantilism renal rickets) is a rarely seen condition observed in infants and children Its chief characteristics are

(1) Renal insufficiency with azotemia

(2) Phosphatemia with elevation of inorganic phosphorous of the blood high above the normal level of from 4 5 to 5 5 mg per 100 cc with a simultaneous relative or absolutely hypocalcemia The normal values of the latter are from 9 to 12 mg per 100 cc

(3) Thinning of the bones (osteoporosis) due to depletion of their calcium content Decalcification may be noted in the diaphysis of the long bones and also in the bones of the calvarium pelvis and vertebrae

(4) Osteoid changes with widening and enlargement of the epiphyses of long bones costochondral junctions clavicles metacarpals phalanges acromial and spinous processes

(5) Stunted physical growth with deflection deformities of the long bones Genu valgum is common Pathologic fractures may occur

Relative to the pathogenesis of renal dwarfism Smyth and Goldman expressed the view that a primary renal disease initiates a chain of pathologic changes that lead to the complex clinical picture In consequence of functional insufficiency of the kidneys retention of phosphorous takes place Phosphatemia in turn stimulates the parathyroid glands and causes parathyroid hyperplasia The latter is followed by demineralization of the bones and by dwarfing Demineralization of the bones is associated with deposition of calcium in the heart arteries and arterioles of various structures and organs of the body

Clinical manifestations of the disease include headache vomiting polyuria except in the terminal stage polydipsia secondary anemia blurred vision due to albuminuric retinitis and convulsions in patients with uremia Hypertrophy and dilatation of the left ventricle is frequent The skin may have an ivory like grayish yellow grayish green color or bronzing It may be coarse and inelastic The urine has low specific gravity and contains slight or large amounts of albumin casts and occasionally evidence of hematuria

There are two features of renal dwarfism which are related to the lungs

(1) Pulmonary hemorrhage

(2) Deposition of calcium in the lung tissue.

Pulmonary hemorrhage is attributable to the low calcium content of the blood and to concurrent high blood pressure A general hemorrhagic tendency may be noted at the same time in the form of purpura of the skin, petechial bleeding in the mucous membranes, epistaxis, melena, and as mentioned before, hematuria Calcifications in the lung tissue may be observed in some of these patients as widely distributed pinhead sized or larger, blotchy areas of calcium deposits throughout both lung fields These changes are readily visualized on the roentgenogram, together with calcification of the pulmonary blood vessels On x ray inspection, pulmonary calcifications, should be distinguished from dense shadows cast by minor or major osteoid changes at the costochondral junctions Multiple nodular calcifications in the lung fields must be *differentiated from healed tuberculosis, fungus infection (aspergillosis,* blastomycosis coccidioidomycosis, histoplasmosis, moniliasis), ascariasis and from widespread minute calcifications seen in some instances of mitral stenosis and scleroderma

The prognosis of renal dwarfism is serious, although in some instances the patient may survive for years

Treatment consists of symptomatic and palliative measures

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EOSINOPHILIC LEUCOCYTOSIS WITH DIFFUSE MILIARY CHANGES IN THE LUNG

By ANDREW L. BANYAI, M.D. and J. WINTHROP PEABODY, M.D.

In 1925, Bass reported a unique clinical picture in a child six years of age, the dominant characteristic of which was marked leucocytosis with eosinophilic cell counts varying between 39 and 70 per cent. Subsequently, he recorded two more identical cases and referred to four additional instances which belong in the same category and which were described by Valledor and his associates in 1939. In five of these seven cases, miliary nodules scattered throughout both lung fields were noted on the roentgenograms. Bass expressed the view that these x-ray shadows were cast by small conglomerations of eosinophilic cells.

Patients in whom these findings were observed were children whose ages varied from two to 11 years. The duration of illness was from several months to six years. During this period, moderate fever was present in some of them which lasted from three to six months. In the others, the disease did not interfere with the comfort of the child. Another characteristic manifestation of this condition was generalized lymphadenophathy most noticeable over the upper one half of the body, especially in the neck and axilla. The lymph nodes varied from pea-sized to marble-sized, were freely moveable, non tender and without tendency to suppuration. Microscopic examination revealed the following: "The conspicuous feature is the large number of eosinophilic leucocytes within the lymph sinuses and, to a lesser extent, within the medullary cords. These leucocytes tend to be clumped in large and small aggregates. Most of them appear to be segmented polymorphonuclear cells, but there are a few staff cells and young forms. In some areas the eosinophils are massed together in sheets, crowding out the other cells. A moderate number of eosinophilic leucocytes are also noted within the connective tissue of the capsule of the node. They are likewise observed within blood vessels (and this is reflected in the blood count). Dispersed between the eosinophils in the sinuses are numerous cells with large nuclei which resemble reticulum cells."

Slight enlargement of the liver and the spleen and coarse rales over the lung were found in some of these patients. The leucocyte count ranged from 20,000 to 70,000 per cubic millimeter. The leucocytosis which was out of proportion to the atoxic condition of the patient, lasted for several months. Interestingly, eosinophilia persisted for years after return of the leucocyte count to normal. Bone marrow studies revealed mye-

loid hyperplasia with predominance of eosinophils

The etiology of this syndrome has not been determined Valledor and his associates attribute it to some hitherto unidentified chronic infection

It is mandatory to differentiate it from eosinophilic leukemia, familial eosinophilia, Hodgkin's disease, Loeffler's syndrome and from conditions associated with eosinophilia and miliary shadows widely distributed in both lung fields as visualized in the roentgenogram These include certain fungus infections, essential pulmonary hemosiderosis, paragonimiasis *periarteritis nodosa, sarcoidosis, schistosomiasis, tropical eosinophilia* and essential primary xanthomatosis

The prognosis is favorable

Treatment consists of symptomatic and supportive measures

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CAVE SICKNESS

By Andrew L Banyai, M D and J Winthrop Peabody, M D

In 1947, Cain and his associates reported on two outbreaks of an acute febrile disease with pulmonary manifestations which occurred on the military reservation at Camp Gruber, Oklahoma Five young men were affected in the first group, and 26 in the second The disease seemed to have causal connection with the men having spent some time in an abandoned storm cellar Washburn and his associates observed 21 white persons of 11 to 55 years of age all male who developed the same condition after having participated in actual excavation work in connection with a treasure hunt in an old abandoned chalk mine in southwestern Arkansas

The etiology of the disease has not been clarified as yet No post mortem studies are available The clinical characteristics are summarized here on the basis of the aforementioned two communications Following a short or moderate exposure and an incubation period of from 5 to 13 days, prodromal symptoms develop in the form of coryza, malaise and muscle aching The prodrome is of 24 to 36 hours duration The incidence of symptoms during the course of the disease is given in the following table

TABLE I

Symptoms	*Percent*
Fever	95 - 100
Sweating	47 - 100
Chest pain	48 - 96
Headache	88 - 95
Coryza	94 7
Chilliness or chills	67 - 84
Cough	73 - 81
Epistaxis	76
Loss of weight	65
Expectoration	53 - 62
Vomiting	43
Nuchal tension	38
Nervous instability	30
Retro-orbital pain	14
Coma	5
Neurologic disturbances	5

The fever is intermittent in character and may reach 106°F (41 1C) It lasts from one to five weeks In some instances, occasional subfebrile elevation of the temperature may be noted during the subsequent six months Chest pain is either substernal, constricting type or it is variable, vague or stabbing The latter is most marked in the region of the costal margin Headache is dull or sharp, throbbing, localized in the frontal area or it may involve the entire head Cough is usually slight or moderate, rarely severe, and it is productive of small or moderate amounts of mucoid or mucopurulent sputum

Abnormal physical findings over the chest are noted in about one third of the cases They consist of scattered areas of dullness, faint breath sounds, sonorous rales and occasional medium sized moist rales. The latter may disappear on coughing

Roentgenograms of the chest reveal numerous areas of dense, discrete infiltrations and consolidations varying from 1 to 20 mm in diameter The x ray opacities show a diffuse, symmetrical distribution in both lung fields, with least involvement in the apexes and at the bases The hilar nodes may or may not be enlarged The pleura is not affected Roentgenologic changes become first noticeable a few days after the onset of illness and reach their maximum intensity in one to two weeks. From then on, they may show gradual clearing or disappear without trace in two months In other instances, the roentgenologic findings remain static at their maximum extent for about two months Their subsequent gradual clearing is followed by permanent diffuse fine fibrosis which becomes discernible in six months after onset of the disease With recovery, the hilar lymph nodes regain their normal size

Laboratory findings are noncontributory Sedimentation rate of the erythrocytes is accelerated The white blood cell count varies from 5 000 to 14,000 with from 32 to 86 per cent polymorphonuclear cells in the differential count No causative pathogens are detectable on examination of the sputum, blood and other body fluids

In the differential diagnosis, one should rule out conditions which cast miliary shadows on the x ray film These are enumerated in the chapter on Pulmonary Manifestations of Collagen Disease Examination of the sputum by a simple smear, culture and animal inoculation, specific skin tests, agglutination and complement fixation tests blood cultures, determination of cold hemagglutinins search for parasites and ova are carried out so as to exclude diseases which may present similar clinical picture These are pneumococcic and tularemic pneumonia

acute interstitial pneumonitis, virus pneumonia, bronchopneumonia, or nithosis, rheumatic fever, influenza, fungus infection, toxoplasmosis, dengue, relapsing fever, malaria, trichinosis, tuberculosis, lymphocytic choriomeningitis

Prognosis

Disappearance of fever and other toxic symptoms may be observed in six to seven days In others, recovery is slow Several weeks may elapse before the temperature returns to normal Even in these cases, fatigue and certain degree of dyspnea was noted to persist for six to seven months

An epidemic of cave borne transitory interstitial pneumonitis was reported in soldiers from Israel In these cases, an incubation period of five to eight days was followed by fever malaise cough, occasional blood-streaked sputum, night attacks of asthma and fever The latter lasted from one to 12 days Physical signs over the lung were scanty The roentgenologically demonstrable pulmonary infiltration disappeared in four or five days The white blood cell count was high in most cases (26,000 per cmm) with eosinophilia which reached 70 per cent The eosinophilia persisted in some instances for several months No etiologic agent was found Loeffler's syndrome and tropical eosinophilia were ruled out

Treatment

Treatment is symptomatic and supportive Penicillin and sulfonamides are of no benefit

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Cave sickness a

PULMONARY XANTHOMATOSIS (HISTIOCYTOSIS)

By Andrew L Banyai, M D and J Winthrop Peabody, M D

Pulmonary xanthomatosis is one of the possible manifestations of generalized xanthomatosis, a term first introduced by Rowland in 1928 Xanthomatosis, which may involve any part or parts of the reticuloendothelial system is characterized by constitutional or localized disturbance of the lipoid metabolism Histologically, the involved sites are comprised of granulation tissue and show the presence of large, bright cells with foamy or vacuolated appearing protoplasm and sharp cell borders, usually referred to as foam cells or xanthoma cells, giant cells and lipoid macrophages In certain types of this disease, a great many eosinophilic cells are seen scattered throughout the affected area The gross appearance of the lesion may be that of multiple sulfur-yellow foci, the color of which is expressed in the term xanthomatosis The latter denotes best the fundamental pathologic changes of this disease and it is preferable to a number of synonyms which have been proposed, such as reticuloendotheliosis, eosinophilic reticuloendotheliosis, lipoidosis, lipoid histiocytosis, lipoid granulomatosis and eosinophilic granulomatosis According to the clinically dominant aspects of xanthomatosis, the following varieties of the disease are recognized according to the combined classification of Sosman and Mallory

(1) Gaucher's disease, which occurs at any age It is a familial disease, most frequent in female children and is fairly benign On account of its chronic course, it may be encountered in adults Its salient features are moderate hepatomegaly and marked splenomegaly, leucopenia, hemorrhagic diathesis and yellowish brown discoloration of the skin Occasionally, skeletal involvement is noted, such as rarefaction of bones and a widening of the lower third of the femur

(2) Niemann-Pick's disease is believed to be an inherited condition It occurs almost entirely in infants of the Jewish race. There is a marked hepatosplenomegaly, associated with rapid enlargement of the abdomen Concurrent pathologic changes are

(a) Moderate to marked enlargement of the superficial lymph nodes,

(b) Pale and yellowish brown discoloration of the skin The alteration of the color of the skin, as well as the sulfur yellow appearance of granular foci elsewhere, is attributed to excessive amounts of carotene

(3) Letterer-Siwe's disease is encountered in infants The usual manifestations are acute onset with fever, skin rash, purpura, anemia

splenomegaly In addition, involvement of bone and enlargement of lymph nodes is demonstrable, with or without deposits of lipids

(4) Hand Schueller Christian disease is a chronic affection which has its highest incidence during the first decade, but it may occur in adults Its typical features are bony defects in the cranium, exophthalmos and diabetes insipidus The latter is due to involvement of the hypophysis Dwarfism and adiposogenital dystrophy are possible accompanying manifestations of hypopituitarism Exophthalmos is caused by pathologic changes in the bones of the orbit The scapula, ribs, pelvic and long bones may also be affected and lymph nodes may be involved On the other hand, there are instances where only one or two aspects of the aforementioned triad are observed Histologically, lipoid granulations occur with or without eosinophilic cells

(5) Eosinophilic granuloma of one or more bones is a rare disease which occurs in children and adults In spite of low grade fever, the patient's general condition is not affected The local lesion may be painful and is associated with leucocytosis and eosinophilia

Thannhauser and Magendantz prefer the designation primary essential xanthomatosis and on the basis of biochemical characteristics, divide this condition into two main categories

(1) Hypercholesteremic type
(2) Normocholesteremic type

In the first category, the following may be noted xanthoma planum and tuberosum, xanthomatous involvement of tendons tendon sheets, wall of the bile ducts (xanthomatous biliary cirrhosis), wall of blood vessels, liver parenchyma, spleen, lymph nodes and endocardium The second category is characterized by possible disseminated xanthomas of the skin mouth, larynx bones, hypophysis tuber cinereum brain, medulla dura matter, spleen liver, lymph nodes, lung and pleura

Epstein and Lorenz demonstrated that there were specific forms of derangements of lipoid metabolism in the various clinically recognized types of xanthomatosis They observed that the lipoids consisted mostly of cerebrosides (kerasin) in Gaucher s disease also that there was an increase in lecithin in Niemann Pick s disease and excess cholesterol in Hand Schueller Christian disease Thannhauser and Magendantz pointed out that xanthomatosis of the hypercholesteremic type is associated with an increase in fat and monoaminophosphatides (lecithin and kephalin) The latter are normal in the normocholesteremic type of xanthomatosis

The etiology of this disease is a much debated issue Pertinent detailed data are available in the monograph of Thannhauser Briefly it may be mentioned that manifestations of xanthomatosis were thought to be caused by embryonal cells which maintain an innate capacity of producing heterogenous fats (Waldeyer, 1871) Virchow classified xanthomatous lesions as tumors This concept has been completely refuted by more recent investigations Chester attributed the disease to infection Others proposed trauma as a provocative factor Pick and Pinkus advanced the view, which is still quite prevalent, that xanthomatosis is due to a constitutional disturbance of the cholesterol metabolism According to Schultz and his associates, some unknown etiologic factor brings about proliferation of the reticuloendothelial cells This is followed by deposition of lipoid and granulomatous fibroblastic proliferation A plausible explanation was offered as to the origin of this disease by Thannhauser who maintains that its underlying cause is a localized intracellular enzymatic disorder of the reticuloendothelial cells This results in the formation of anomalous lipids which constitute the pathologic essence of xanthomatosis

Symptomatology

It is beyond the scope of this chapter to discuss the symptoms of xanthomatosis in general The variable localization and extent of the disease implies great variations in symptoms as well as in clinical findings Affection of the long bones may lead to weakness and stiffness in the extremities and to inability to walk Involvement of the vertebrae is bound to result in pain at the site of the lesion, such as low back pain which may or may not radiate into both lower extremities In addition to such clinical manifestations as brought about by the particular type of xanthomatosis pulmonary involvement is associated with complaints referable to the chest These are

(1) Cough which is usually dry or productive of small amounts of mucoid sputum

(2) Dyspnea

(3) Pain in the chest

The first case of pulmonary involvement in xanthomatosis was recorded by Pusey and Johnstone in 1908 Since then, pulmonary lesions are reported with increasing frequency Their detection is predicated upon the diagnostic acumen and freedom from diagnostic preoccupation of the examining physician Pathologic changes are found virtually in all cases that come to necropsy They consist of destruction of interalveolar

septums and infiltration of the interstitial tissue with granulomatous proliferation When diffuse fibrosis is present, not only alveoli but also smaller bronchi, become obliterated There are instances where thoracic symptoms are entirely absent in spite of roentgenologically demonstrable affection of the lung Troxler and Niemetz recorded the case of a 35 year old white man in whom xanthomatosis caused bone lesions, hypopyseal manifestations and pulmonary changes The latter were complicated by spontaneous pneumothorax apparently due to xanthomatous involvement of the visceral pleura Other possible complications include mediastinal emphysema and atelectasis brought about by cysts of the lung

Diagnosis

With proper interpretation of findings on physical x ray and laboratory examinations arriving at a correct diagnosis of essential xanthomatosis is not difficult It is mandatory to secure a biopsy specimen for microscopic studies when a bone lesion is accessible or enlarged lymph nodes or skin changes of suggestive appearance are found There are no characteristic hematologic findings except slight or moderate eosinophilia in some instances Examination of the bone marrow from the sternum, iliac crest or one of the lumbar spinous processes reveals the characteristic foam cells

Roentgenograms of the bones reveal single or multiple areas of round or irregular rarefaction, cyst like zones which may resemble defects caused by osteomyelitis On x ray examination of the lung two types of alterations can be observed

(1) In the early phase of the disease there are numerous small nodular shadows evenly distributed throughout both sides or mainly in the upper lung fields

(2) In the late stages one finds diffuse pulmonary fibrosis without nodulation Also at this stage the presence of emphysema becomes evident The hilar shadows may be enlarged in either phase of the disease

In the differential diagnostic evaluation of findings suggestive of primary essential xanthomatosis of the lung one should rule out conditions which may cause widespread miliary shadows on the roentgenogram A list of such diseases is given in connection with the discussion of Pulmonary Manifestations of Lupus Erythematosus Also, it is of utmost importance to exclude other pathologic states associated with roentgenologically demonstrable diffuse fibrosis of the lung The latter

may result from tuberculosis, from a number of other infections of bacterial, rickettsial or virus origin and also from massive inhalation of noxious fumes, gases and dusts

Prognosis

The course of the disease can be gauged according to the pathologic phase and extent of the disease Fortunately, it has been definitely established that Hand Schueller Christian disease and eosinophilic granuloma of the bone can be effectively treated

Treatment

The management of patients with essential xanthomatosis should be planned with three purposes in mind

(1) Adequate measures for the control of hypopituitarism,

(2) Prompt treatment of focal lesions, with particular attention to x ray irradiation of the hypophysis, bone and skin lesions,

(3) General supportive measures in the form of nutritious, balanced diet, vitamin supplements, if necessary, and correction of anemia, symptomatic medication

Retrogression of pulmonary xanthomatous lesions can be anticipated from x ray irradiation of the lung in the early miliary form of the disease When fibrosis is firmly established, x ray therapy to the lungs serves no purpose Equivocal results were observed by Blahd and his associates with the use of cortisone Essential pulmonary xanthomatosis associated with eosinophilic granuloma of the bone was first reported by Weinstein and his associates They observed considerable decrease in the nodular infiltration of the lung after a series of x ray irradiations to this organ Also, others used x ray therapy to the lungs with satisfactory therapeutic results in other forms of essential primary xanthomatosis

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PRIMARY AMYLOIDOSIS OF THE LUNG

By ANDREW L BANYAI, M D and J WINTHROP PEABODY, M D

The term amyloidosis is usually associated with a systemic disease which is secondary to long standing diseases complicated by suppuration Tuberculosis has been considered its most common cause According to Rosenblatt, the incidence of secondary amyloidosis among patients with pulmonary tuberculosis was 24 4 per cent on postmortem examination while in other forms of chronic diseases it was only 1 2 per cent Diseases other than tuberculosis which may be complicated by amyloidosis include chronic suppurative osteomyelitis (a condition which is becoming rather infrequent on account of modern chemotherapeutic and antibiotic treatment), ulcerating tumors, lung abscess, bronchiectasis, pyelonephritis and others Suppuration is not a prerequisite of generalized amyloidosis Cases have been reported in syphilis, Hodgkin's disease, silicosis, leukemia, myelomata, arthritis and rheumatic heart disease

The designation of this condition as amyloidosis (first proposed by Virchow) is misleading in that it imparts the idea of pathologic changes having something to do with starch This is, however, not the case Chemically amyloid is a complex protein, an albuminoid substance and therefore, properly the disease should be referred to as albuminoidosis Originally, it was known as lardaceous disease The change in terminology was brought about by the blue color reaction given amyloid substance when brought in contact with a watery solution of iodine The same color reaction obtains between starch and iodine solution

Pathologically, amyloidosis is characterized by the impregnation with this substance of connective tissue fibers in the vessels walls and intercellular deposition in the parenchyma of various organs

Primary amyloidosis is extremely rare Dillon and Evans reported that at the Peter Bent Brigham Hospital there were only three such cases found out of 4,551 necropsies performed during a period of 28 years Dahlin in 1949 noted that only 60 cases of primary amyloidosis were recorded in the medical literature, including 6 reported by himself since the first case report of Wilks in 1856 Higgins discussed 48 cases reported by Eisen and 23 others which had been reported since Its distinguishing chracteristics are according to Lubarsch

(1) The absence of chronic disease in association of which amyloidosis may occur

(2) The development of amyloidosis in organs in which the appearance of amyloidosis is uncommon, such as the heart, lung skin

(3) The almost complete freedom from amyloidosis in organs which usually are considered its predilectional sites such as the liver spleen kidneys and suprarenal glands

(4) Occasional tumor like manifestation of this condition

(5) The involved tissues often fail to show the staining reactions typical of amyloidosis

Primary amyloidosis may manifest itself in the involvement of mesodermal structures in the form of a generalized disease or it may be localized predominantly to one or two organs Balser noted stenosis of the trachea and major bronchi due to amyloid changes in the walls of these structures In addition to these changes Glockner observed tumor like formations caused by localized amyloidosis in the larynx trachea and large bronchi Also Schottenfeld and his collaborators noted localized deposition of amyloid substance in the walls of the trachea and major bronchi The consequent narrowing of the respective air passages results in wheezing and dyspnea Diagnosis is established by examination of bronchoscopically removed biopsy specimen Superimposed secondary infection with bronchopneumonia or bronchiectasis may aggravate the condition and may prove fatal

Of the 54 instances of primary amyloidosis investigated at necropsy pulmonary involvement was present in 24 A composite picture of the pathologic findings can be given from the reports of Sappington Davie and Horneff and of Dirkse The lung shows an increased consistency due indurated ill defined nodules and strands The cut surface of the lung may give the appearance of honeycombing The hilar lymph nodes are enlarged hard in consistency and surrounded by and transformed into heavy fibrous tissue The fibrosis extends along the mediastinum bronchi and large pulmonary vessels In addition changes may be noted on the pleura in the form of thickening adhesions or effusion The latter is clear and serous in character Possible concomitant pathologic findings are enlargement of the spleen amyloid involvement of the heart muscle and valves the suprarenal glands skin cervical axillary and inguinal lymph nodes Histologically there is a universal amyloid infiltration of the walls of the arteries and veins in the lung with heavy amyloid changes of the alveolar walls and lung septa Weismann and his associates reported a case with primary pulmonary amyloidosis After total pneumonectomy of the right lung a hard leathery irregular infiltrating whitish yellow mass was found at the hilum The walls of the main bronchus and its immediate branches were infiltrated with amyloid substance

with resulting loss of flexibility and lack of cilia These changes led to the development of bronchiectasis in the distal bronchi and consequent repeated pulmonary hemorrhages

Symptoms of primary amyloidosis of the lung develop insidiously and consist of dyspnea, non-productive cough, easy fatigability and occasional chest pain There is no loss of weight General toxic symptoms are absent The dyspnea is explainable on the basis of the great thickening of the pulmonary vessel walls in consequence of which the lumen is markedly reduced This change, together with a thickening of the alveolar walls, renders normal oxygen intake and carbon dioxide elimination impossible Progression of amyloidosis in the lung is associated with a gradually increasing dyspnea

The diagnosis is arrived at on the basis of ruling out diseases with a similar symptoms and roentgenologic findings, of biopsy of accessible involvements (lymph node, skin) and of the Congo red test first used by Bennhold in 1923 The roentgenogram of the chest shows an enlargement of the hilar lymph nodes, accentuation of the linear markings, with or without a ground glass appearance of the lung fields and widely distributed nodules in both lungs These findings call for differentiation from conditions which may cast nodular shadows in the roentgenogram of the chest Their list is given in the chapter on Pulmonary Manifestations of Collagen Disease

In addition to biopsy studies wherever possible, the Congo red test is used for a conclusive clinical diagnosis A positive Congo red test in itself is sufficient for establishing the diagnosis A negative test is found in about 50 per cent of the cases The test is based on the observation that intravenously injected Congo red rapidly disappears from the blood stream and on account of its special affinity, it is deposited in tissues with amyloid changes In normal individuals, on the other hand, it is excreted through the kidneys and imparts to the urine a deep red color The standardized colorimetric test of Taran and Eckstein consists of the following steps

"Inject 1 cc of a 1 per cent acqueous solution of Congo red per 10 pounds of body weight intravenously At the end of exactly four minutes, and then one hour, after the injection, obtain blood specimens of 10 cc each and place them into clean, dry test tubes Allow the bloods to clot and retract and then centrifuge them at a moderate speed for 10 minutes Aspirate off the clear sera into graduated centrifuge tubes Add acetone equal to the volume of serum in each tube and shake them

well Centrifuge the tubes for 10 minutes at a moderate speed Pour off the supernatant fluids and place them into micro cups of a colorimeter to be compared Set the four minute specimen at 20 mm and read the one hour specimen Calculation

$$100-\left(\frac{\text{Reading of 4 minute specimen}}{\text{Reading of 1 hour specimen}}\times 100\right)=\text{percent absorption}$$

Using this procedure, amyloidosis is diagnosed when the absorption of Congo red is 100 per cent on two consecutive examinations The latter criterion was suggested by Selikoff in 1947 on the basis of extensive clinical and necropsy studies Also, he pointed out the occurrence of false negative tests in nearly 25 per cent of generalized secondary amyloidosis with less than 90 per cent absorption of Congo red The Bennhold test is likely to be negative in patients with localized amyloid mass in the lung

Primary pulmonary amyloidosis is a fatal disease It may progress rapidly or its course may extend from two to ten years The treatment is palliative when the pathologic process extensively involves both lungs Solitary localized amyloid mass calls for surgical removal by resection Recovery followed total pneumonectomy in a patient of Weismann and his associates The administration of liver substance is of possible therapeutic value in widespread disease

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CHAPTER XX

DISEASES OF THE MEDIASTINUM

By NORMAN J WILSON, M D *and* RICHARD H OVERHOLT, M D

INTRODUCTION

In this chapter no attempt will be made to enter into excessive detail or to be complete in the discussion of the various affections of the mediastinum Instead, fundamental concepts and the clinical approach to the most common and important types of mediastinal pathology will be emphasized The related anatomy and pathological physiology will be briefly discussed Diseases of the heart, great vessels and esophagus have not been included

The authors have used the publications listed in the bibliography liberally in preparing this chapter The reader is referred to these for more detailed and more complete coverage of diseases of the mediastinum

ANATOMY

The mediastinum is that part of the thoracic cavity lying between the two pleural sacs It is bounded anteriorly by the sternum, posteriorly by the thoracic vertebrae, laterally by the mediastinal pleura, and inferiorly by the diaphragm Superiorly the mediastinum has no true anatomical boundary, but terminates at the superior aperture of the thorax This is an important anatomical consideration because through the superior aperture pass many vital structures shared by both the neck and mediastinum In addition it permits the descent of certain tumors, especially goiters, from the neck into the mediastinum and establishes continuity between the mediastinum and certain fascial spaces of the neck As will be seen later this is a common pathway for the extension of infection from the neck into the mediastinum

Anatomical Division of the Mediastinum

Anatomically, the mediastinum is divided into two major compartments, the superior and inferior The inferior mediastinum is further subdivided into anterior middle and posterior parts

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thymus pericardium heart diaphragm and upper surface of the liver They also receive afferent trunks from the sternal nodes which in turn drain the anterior chest wall and medial portion of the breast The efferent trunks from these nodes join with those of the tracheobronchial nodes to form the right and left bronchomediastinal trunks

2 POSTERIOR MEDIASTINAL NODES

These are located along the aorta and drain especially the esophagus and diaphragm Their efferent trunks end largely in the thoracic duct, but some join the tracheobronchial nodes

3 TRACHEOBRONCHIAL NODES

a Lateral tracheobronchial — Lateral to the trachea close to the angle between the trachea and the main bronchi

b Inferior tracheobronchial (infracarinal)—These lie just beneath the bifurcation of the trachea

c Bronchopulmonary — In the hilum of each lung

The tracheobronchial nodes drain the lymphatics from the entire lung and pleura They eventually drain into the bronchomediastinal lymph trunks and finally enter the venous system near the junction of the internal jugular and subclavian vein either separately or in con junction with the jugular and subclavian lymphatic trunks Thus the tracheobronchial lymphatics are intimately associated with those of the cervical chains This explains the frequent involvement of the supra clavicular nodes secondary to carcinoma within the lung or mediastinum

Since the tracheobronchial lymph nodes drain the lungs and pleura they are usually involved secondary to pulmonary and pleural infection Frequently this is of little clinical significance However it must be kept in mind that apparently benign lymphadenopathy seen in certain inter stitial pneumonias such as those associated with measles pertussis and influenza may choke the bronchi and cause various degrees of bron chial occlusion This leads to the development of bronchiectasis in a certain percentage of such cases The tracheobronchial nodes are always involved significantly during a primary tuberculous infection of the lung whether it occurs during childhood or adulthood They are seldom enlarged secondary to the re infection type of tuberculous infection ex cept in the pigmented races especially the negro

The mediastinal lymphatics are often involved by the time a diag nosis has been made when any of the intrathoracic structures are in volved by a primary carcinoma They are also frequently involved secondary to metastatic carcinoma of the lung since the lung is so

The superior mediastinum extends from the superior aperture of the thorax to the inferior border of the manubrium anteriorly and the 4th thoracic vertebra posteriorly Since certain tumors tend to occur either anteriorly or posteriorly, it is helpful for clinical purposes to divide the space into anterior and posterior portions, the partition between these being a plane passing just anterior to the trachea

The inferior mediastinum extends from the angle of the sternum in the front and the 4th vertebral body behind to the diaphragm The anterior mediastinum lies between the sternum and pericardium, the middle mediastinum lies between the level of the anterior and posterior layers of the pericardium, the posterior mediastinum lies between the posterior layer of the pericardium and the thoracic vertebrae

Clinical Division of the Mediastinum

Clinically, it is more simple and helpful to use the cardiac shadow as a basis for dividing the mediastinum into its various parts as follows The superior mediastinum is that portion lying above the cardiac shadow the middle mediastinum contains the heart shadow, and the anterior and posterior portions of the mediastinum lie in front and behind it respectively

Contents of the Various Mediastinal Compartments

Superior Mediastinum

Trachea, esophagus, thymus gland, great vessels thoracic duct, the vagi, left recurrent laryngeal nerve, phrenic nerves and sympathetic trunks

Anterior Mediastinum

Areolar tissue and a few lymph nodes

Middle Mediastinum

Heart and pericardium, ascending aorta, pulmonary vessels lower portion of the superior vena cava terminal portion of the azygos vein the main bronchi and the phrenic nerves

Posterior Mediastinum

Descending aorta, azygos vein, thoracic duct, esophagus and lymph nodes

Lymphatics of Mediastinum

There are three main groups of visceral nodes in the mediastinum

1 Anterior Mediastinal Nodes

These are located along the anterior surface of the arch of the aorta and also lower in the anterior mediastinum They drain the thyroid

thymus pericardium, heart, diaphragm and upper surface of the liver They also receive afferent trunks from the sternal nodes which in turn drain the anterior chest wall and medial portion of the breast The efferent trunks from these nodes join with those of the tracheobronchial nodes to form the right and left bronchomediastinal trunks

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commonly the site of metastases Lymphatic extension into the mediastinum may occur from the breast and cervical lymphatics Metastatic sarcoma is rare in the mediastinal lymph nodes, as is true in lymph nodes elsewhere in the body Lymphomas are one of the most common causes of mediastinal lymphadenopathy The mediastinal nodes may also be enlarged in infectious mononucleosis Sarcoidosis usually causes a characteristic type of lymphadenopathy involving the peribronchial nodes bilaterally and also the right peritracheal nodes It is frequently associated with diffuse nodular and reticular infiltration in the lungs The lymph node enlargement in erythema nodosum is very similar to that caused by sarcoidosis and differential diagnosis by x ray alone may *be impossible*

General Considerations

Normally, the mediastinum is a mobile partition between the two lungs, changing its shape with each phase of the respiratory cycle and with changes of position of the body It elongates and narrows during inspiration and foreshortens and widens during expiration as a result of the descent and ascent of the diaphragm, respectively It also *shifts* slightly to the dependent side in the position of lateral recumbency *The* prone position causes increased width of the mediastinum *Its shape* and width vary in the antero-posterior as compared with the conventional postero-anterior position These facts make it imperative when interpreting roentgenograms that one know the position of the patient and the phase of respiration during which the x ray was taken

The normal mediastinum *occupies the central position in* the thorax *by virtue of equal pressures in the two pleural* cavities Anything that upsets this equality of pressures will cause deviation of the mediastinum Atelectasis causes increased negative pressures and results in shifting of *the mediastinum toward the affected side A shift* toward the unaffected side is usually due to the accumulation of fluid or air in the pleural space which reduces the negative intrapleural pressure or may actually make it positive *Permanent* retraction of the mediastinum occurs as a result of chronic fibrous disease in the lung obliterative *pleuritis em*pyema and following pneumonectomy and re expansion *of pneumo*thorax Not infrequently permanent *mediastinal shift is associated* with symptoms so severe that *a thoracoplasty is indicated* to overcome the *displacement of and correct the* abnormal pull on the mediastinal structures *When the mediastinal* pleura becomes thickened because of re

action to infection or tumor, the mediastinum may become fixed and no longer capable of responding to changing intrapleural pressures.

At times actual herniation of the lung through the so-called "weak spots" of the mediastinal pleura and lung through the so-called "weak spots" of the mediastinum may occur, especially with pneumothorax. These "weak spots" represent areas devoid of contents so that the right and left layers of the mediastinal pleura come in contact. One is located in the antero superior mediastinum between the sternum and pericardium from the level of the 2nd to the 4th costal cartilage. The other is in the inferior part of the posterior mediastinum between the esophagus and the aorta. Maier has called attention to a similar area lying between the esophagus and the 3rd to the 5th dorsal vertebrae.

Because of the sternum in front and the vertebral bodies and ribs posteriorly, the mediastinum does not lend itself well to physical examination. A widening by percussion is one of the few worthwhile signs that may be elicited. The only other significant physical findings are those secondary to pressure on or involvement of one of the mediastinal structures, such as a paralyzed vocal cord, dilated superficial veins, etc.

Roentgenography and fluoroscopy are essential in the diagnosis and evaluation of mediastinal pathology. In fact, a high percentage of mediastinal tumors seen in practice are discovered by x ray at a time when they are causing no significant signs or symptoms (silent lesion). It cannot be stressed too strongly that any single projection, including the usual postero-anterior single or stereoscopic views, represent an inadequate study of the mediastinum. Routine and over-exposed postero-anterior and lateral projections are the minimum required and frequently oblique views are necessary to clearly demonstrate the lesion. This is due to the fact that the densities of the vascular and bony structures of the mediastinum may become superimposed upon that of the pathology in any one projection and completely obscure it. This is especially true of tumors that tend to lie in the midline, such as bronchogenic cysts and thymomas. These may be seen only in the lateral roentgenogram.

The mediastinum is unique in that it contains so many vital structures in such a small space. These structures are representative of the respiratory, circulatory, gastro intestinal, lymphatic and nervous systems. Any of these may, and frequently are, involved secondary to infections or tumors of the mediastinum. It is important that treatment be instituted in such conditions before irreparable damage has occurred to the surrounding vital structures.

MEDIASTINAL EMPHYSEMA

Mediastinal emphysema indicates the presence of air in the mediastinum. As a rule, this is a *benign* condition because the air is not under increased pressure and, therefore, causes no marked physiological disturbance. The diagnosis here is of importance to enable a physician to follow the patient intelligently and to avoid confusion with other clinical conditions which mediastinal emphysema may mimic, especially coronary occlusion. At times, however, the air accumulates under increased pressure with resulting grave physiological disturbances—the *malignant* type. Then the correct diagnosis becomes imperative because prompt surgical treatment is required to save the patient's life.

Etiology

Air may enter the mediastinum by four routes: (1) Along the fascial planes of the neck following such conditions as deep wounds of the neck or pharynx and puncture of the maxillary sinuses, (2) from the retroperitoneal space through the diaphragmatic orifices secondary to ruptured hollow visci and the following pneumoperitoneum or perirenal air insufflation, (3) through a perforation of the trachea, main bronchi or esophagus, directly into the mediastinum, and (4) secondary to interstitial emphysema of the lung which resulted from rupture of the pulmonary alveoli.

Although the first three routes mentioned above are well recognized, the most common cause of mediastinal emphysema is ruptured alveoli with resultant interstitial emphysema of the lung. In fact, as the Macklins have pointed out, this condition is seldom seen without an associated interstitial emphysema, even though the latter may go unrecognized.

There are essentially two causes of ruptured alveoli: (1) direct injury to the alveoli as seen following the induction of pneumothorax, penetrating wounds and rib fracture, (2) increased pulmonary pressure associated with such conditions as childbirth, heavy lifting, positive pressure anesthesia, asthma, pertussis and any cause of bronchial occlusion such as tumor, tuberculosis, foreign body or a mucus plug.

Hamman first described mediastinal emphysema as a result of spontaneous rupture of the alveoli. The cause is not clear since in many cases there is no evident precipitating factor. The alveoli rupture apparently, in the presence of normal intrabronchial pressures. Since these attacks tend to recur, an inherited defect in tissue quality has been suggested as a possible etiological factor.

When air escapes from the ruptured alveoli, it travels along the vascular structures of the lung, thence through the hilum into the mediastinum. Air may escape from the mediastinum by one or more of three pathways. First, it may escape into the deep and subcutaneous tissues of the neck, producing subcutaneous emphysema, the presence of which is usually evidence of mediastinal emphysema. The second pathway of escape may be through the diaphragm into the retroperitoneal tissues. The third route of escape of air from the mediastinum is into the pleural cavity through a rupture of the mediastinal pleura. This may occur unilaterally or bilaterally. Hamman believes that this is the most common mechanism producing tension pneumothorax following chest injury and serves best to explain the case of contralateral pneumothorax (contracoup pneumothorax). It is a peculiar fact that air rarely, if ever, enters the mediastinum from the pleural cavities, whereas the reverse seems to occur frequently.

Pathological Physiology

When a small amount of air gains entrance to the mediastinum, or when a large amount of air finds an adequate avenue of escape as evidenced by subcutaneous emphysema, there is little, if any, physiological disturbance because the mediastinal pressure is not increased. As a result, few or no significant symptoms are associated with this *benign type* of mediastinal emphysema. However, when a large amount of air becomes trapped in the mediastinum, the mediastinal tension becomes increased and produces serious physiological disturbances — *malignant* mediastinal emphysema. The outstanding effect is collapse of the veins with resulting impairment of the return of blood to the heart. The associated interstitial emphysema also causes collapse of the pulmonary vessels causing venous stasis and interfering with the escape of air during expiration. As a result of these factors circulation becomes impeded and oxygen exchange impaired. If these conditions are permitted to progress, they cause death.

Clinical Manifestations

The clinical manifestations of mediastinal emphysema are apt to vary considerably, depending upon the cause, type and associated pathology. For instance, in the benign type there may be few or no symptoms. At times there may be severe substernal pain often leading to the diagnosis of coronary occlusion. There may be an associated pneumothorax with its signs and symptoms. In those cases resulting from traumatic or

spontaneous rupture of the esophagus, the severe symptoms of the accompanying mediastinitis are apt to overshadow any symptoms produced by the emphysema

However, there are certain clinical manifestations of mediastinal emphysema per se to permit a correct diagnosis in the majority of cases Substernal and chest pain are common On physical examination the cardiac dullness may be obliterated by the overlying air A peculiar crunching sound (Hamman's sign) is often heard over the precordium synchronous with systole Subcutaneous emphysema may be present in the cervical region or, at times, involving large portions of the body surface The patient may complain of abdominal pain if air has extended into the retroperitoneal space If the mediastinal air is under tension, there will be dyspnea, cyanosis engorged veins and eventually circulatory failure

The roentgenograms frequently reveal areas of radiolucency along the borders of the superior mediastinum and at times along the cardiac borders The lateral projection often reveals air between the heart and the sternum Air is usually seen in the fascial planes of the neck and may be present in the pleural cavity and retrocardiac spaces

Treatment

The benign type of mediastinal emphysema requires no active therapy The patient's blood pressure and pulse should be watched carefully, however, to make sure that increased mediastinal tension does not develop

The malignant type requires immediate treatment which consists of, (1) sedation to relieve the pain, (2) oxygen to relieve the dyspnea and cyanosis, and (3) surgical drainage of the mediastinum to provide an outlet for the entrapped air, and thus reduce the mediastinal tension The surgical approach is through the neck above the suprasternal notch entering the mediastinum anterior to the vascular structures At times intermittent suction by means of an improvised cup over the incision is required When indicated, this surgical procedure is life saving

MEDIASTINITIS

Incidence

Mediastinitis was not a common type of infection even before the era of the antibiotics However, since the advent of the antibiotics, especially penicillin, it has become distinctly uncommon Now, one rarely

sees the enlarged mediastinal lymph nodes secondary to pulmonary and pleural infection If they are involved, they rarely suppurate and break down The occurrence of mediastinitis has been reduced also by a lowered incidence of many of the conditions that used to be common etiological factors, such as empyema, lung abscess and subphrenic abscess At present, the antibiotics prevent, as a rule, extension of infection into the fascial planes of the neck in such conditions as tonsillitis, pharyngitis, dental abscess and infection of the parotid gland — one of the most common causes of mediastinitis prior to the use of these drugs The use of streptomycin in the therapy of pulmonary tuberculosis has reduced all extrapulmonary extensions associated with this disease, including mediastinitis It is interesting that mediastinitis rarely occurs as a complication of intrathoracic surgery, except that upon the esophagus The one type of mediastinitis that is still seen with some frequency is that resulting from rupture of the esophagus which is due in the vast majority of instances to trauma from foreign bodies or instrumentation This is the etiological factor in about fifty per cent or sixty per cent of cases

Routes of Infection

Infection usually reaches the mediastinum by one of three routes (1) the lymphatics, (2) direct extension from structures in or adjacent to it, and (3) extension from the fascial planes in the neck The latter is the most common by far, representing the avenue of infection in about seventy to 75 per cent For this reason a clear concept of the anatomy of the fascial spaces of the neck and their relation to the mediastinum is important

Anatomy of the Fascial Planes of the Neck

The prevertebral and pretracheal fascias form the boundaries of the viscerovascular space of the neck and divide it into three compartments (1) the visceral space, (2) the previsceral space, and (3) the retrovisceral space

The prevertebral fascia lies between the prevertebral muscles posteriorly and the pharynx, great vessels and esophagus anteriorly

The pretracheal fascia splits to enclose the sternomastoid muscle, forms part of the carotid sheath laterally and extends anterior to the larynx and trachea It continues posteriorly to form the bucco-pharyngeal fascia and descends into the mediastinum to blend with the covering of the aorta and pericardium

The viscero vascular space is contained within these two fascial layers and extends from the base of the skull to the level of the bifurcation of the trachea This space is divided into three compartments as follows (1) *Visceral space* This compartment lies between the pretracheal and the bucco pharyngeal fascias It is bounded laterally by the carotid sheaths Between the pretracheal fascia and the trachea there is a separate small space, the *pretracheal space* The visceral space contains the thyroid, trachea and esophagus Infection of the mediastinum by this route is not common (2) *Previsceral space* This space lies between the sternothyroid and sternohyoid muscles anteriorly and the pretracheal fascia posteriorly Infection does not extend into the mediastinum from this space because of the attachment of the fascia to the sternum (3) *Retrovisceral space* This space lies between the bucco pharyngeal fascia and the prevertebral fascia and is limited laterally by the carotid sheaths The important anatomical fact to be emphasized here is that the bucco pharyngeal fascia is the only structure separating this space from the pharynx and esophagus predisposing this space to infection when perforation of these structures occurs Occasionally this space may be involved by a paravertebral abscess which ruptures through the prevertebral fascia

In addition to the above the carotid sheath may direct infection into the mediastinum secondary to infection to the parapharyngeal region

Classification

Mediastinitis is classified usually as acute non suppurative acute suppurative and chronic

1 ACUTE NON SUPPURATIVE MEDIASTINITIS

As a rule, this is little more than a lymphadenitis with some inflammation of surrounding tissues secondary to infections of the neck and adjacent thoracic structures It is rarely of clinical significance and is seen less frequently now since the antibiotics have been used in the treatment of the primary infection

2 ACUTE SUPPURATIVE MEDIASTINITIS

Acute suppurative mediastinitis is the most important clinical type and may be either a diffuse phlegmonous infection or result in a localized abscess The phlegmonous type is usually the result of a fulminating infection descending into the mediastinum from the fascial planes of the neck, usually the retrovisceral space The pathology consists of a diffuse inflammatory process characterized by induration edema and localized areas of necrosis The posterior mediastinum is usually most

involved When associated with esophageal perforation, the process is especially virulent due to the overwhelming aerobic and anaerobic infection which may cause an actual gangrene in the mediastinal tissues

Mediastinal abscess is usually located in the superior mediastinum and represents extension of suppuration from the cervical spaces

When infection descends from the cervical fascial planes into the mediastinum, the aortic arch usually directs it more to the right than to the left side For this reason abscesses tend to form on the right side and the right pleura is more commonly involved This may result in a sympathetic pleural effusion or actual empyema

3 Chronic Mediastinitis

This term usually refers to a diffuse cicatrizing type of mediastinitis It is at times difficult to be sure of the etiological factor but it may result from tuberculosis rheumatic fever syphilis or pre existing acute mediastinitis At times chronic mediastinitis refers to specific infection such as actinomycosis and tuberculosis Because of the extensive fibrosis the manifestations of this malady are secondary to retraction or constriction of the various mediastinal structures Involvement of the mediastinal veins is most common but paralysis of the recurrent nerves and stenosis of trachea bronchi and esophagus may result Mediastino-pericarditis and esophageal diverticulum may also be associated The only common cause of chronic abscess in the mediastinum is tuberculosis This usually results from an extension of infection of the parasternal nodes anteriorly or a paravertebral abscess posteriorly

Diagnosis

In the nonsuppurative type of acute mediastinitis symptoms due to the mediastinitis are apt to be mild and overshadowed by the primary infection As pointed out before this type is rarely of clinical significance and is less commonly seen because of the use of antibiotics Symptoms consist of those secondary to infection such as chills and fever and possibly others as a result of disturbed function of the mediastinal organs such as dyspnea dyphagia and hoarseness The roentgenogram may show widening of the mediastinal shadow

Acute suppurative mediastinitis, especially that due to rupture of the esophagus is associated with severe local and systemic symptoms As a rule the patient will be toxic with high fever and marked leukocytosis Substernal pain is a constant complaint Since esophageal perforation is most common at the cricopharyngeus, pain tenderness swelling and

evidence of emphysema are commonly found in the cervical region Symptoms secondary to mediastinal compression and disturbed function of the mediastinal organs are common The x ray will show widening of the mediastinum and, in the case of esophageal perforation, evidence of emphysema both in the neck and mediastinum Mediastinal abscess is located, as a rule, in the superior mediastinum and usually presents at the right side of the sternum The trachea is commonly displaced anteriorly and the retrotracheal space widened

Treatment

The treatment of *subacute mediastinitis* is that of the primary infection There is no satisfactory therapy for *chronic mediastinitis*, the care of such patients consisting of symptomatic care and at times treatment of the etiological disease, such as syphilis Decompression operations have been tried to relieve symptoms but have not proved successful in most instances

The treatment of *acute suppurative mediastinitis* is an entirely different problem Here, prompt and energetic treatment is essential If secondary to esophageal perforation, the esophagus is placed at complete rest, nothing being given by mouth Parenteral feedings are usually sufficient to maintain nutrition Rarely will a gastrostomy be necessary Prior to the days of the antibiotics it was generally accepted that prompt surgical drainage was indicated in any suppurative process involving the mediastinum or retrovisceral space of the neck, especially when the result of esophageal perforation However, since the advent of the potent antibiotics now available, the clinical approach is not so clear cut and definite as it was Not infrequently, early acute infections of the fascial spaces of the neck and the mediastinum respond to extremely high doses of the antibiotics In fact, the last two esophageal perforations seen by the authors, have both been treated successfully without operation One patient had mediastinitis secondary to perforation of the esophagus with an esophagoscope, the other with the gastroscope The only danger with this approach to therapy is that it might be continued in spite of arising indications for surgical drainage When the patient's fever, toxemia and clinical condition do not respond promptly to medication, when there is any x ray or physical evidence of extension of infection especially in the neck, or when there is definite evidence of a localized abscess, drainage should be instituted immediately If the infection is localized above the fourth vertebral

body, adequate drainage can be accomplished through an incision in the neck along the anterior border of the sternomastoid If the infection is below this level, a posterior mediastinotomy must be performed This consists of resecting one or more ribs along with the transverse processes and entering the mediastinum by the extrapleural route

MEDIASTINAL TUMORS

Classification and Clinical Approach

The following is the classification of Heuer and Andrus

A *Cysts*
  1 Dermoid
  2 Teratoma
  3 Cyst of endodermal origin
  4 Cyst of mesodermal origin
  5 Cystic lymphangioma
  6 Echinococcus cyst
B *Connective Tissue Tumors*
  1 Fibroma
  2 Lipoma
  3 Leiomyoma
  4 Xanthoma
  5 Chondroma
  6 Chondromyxoma
  7 Chondrosarcoma
C *Neurogenic Tumors*
  1 Neurofibroma
  2 Ganglioneuroma
  3 Neuroblastoma
  4 Neuroepithelioma
D *Benign and Malignant Tumors of Thymus*
E *Primary Tumors of Mediastinal Lymph Nodes*
  1 Lymphosarcoma
  2 Hodgkin's Disease
  3 Endothelioma
F *Sarcoma (Primary and Secondary)*
G *Carcinoma (Primary and Secondary)*
H *Intrathoracic Goiter*

In addition to this classification must be added such rare types of tumor as the hemangioma, aortic body tumor, pheochromocytom

tuberculoma, granuloma, parathyroid tumor, and mediastinal meningocele

It becomes apparent from this classification that mediastinal tumors constitute a complex pathological problem However, the clinical approach to these tumors can be greatly simplified since they fall into three general groups from the therapeutic standpoint

1 THE LYMPHOMA

This is treated by deep x ray therapy It does not lend itself to surgical removal

2 METASTATIC TUMOR

The primary malignancy is usually evident, although at times the metastases overshadow a small primary tumor The only possible treatment here is palliative x ray therapy

3 PRIMARY MEDIASTINAL TUMOR

Unless there is unmistakable evidence of malignant extension such as a positive biopsy of a cervical node, all primary mediastinal tumors should be explored and removed unless the age and general condition of the patient contraindicate the operation

It is an established clinical fact that surgical removal is safer than the threat of such tumors under "careful observation" The majority of mediastinal tumors are initially benign, but all have malignant potentialities in that they will usually produce serious symptoms or death by one of the following mechanisms

1 Pressure on the vital organs of the mediastinum

2 Infection with the possible sequellae of mediastinitis, empyema or pulmonary infection

3 Malignant degeneration

This is common in mediastinal tumors There are no reliable clinical or roentgenological signs to determine whether or not malignant changes have taken place — a fact which emphasizes the need for surgical extirpation

Primary Mediastinal Tumor

Although aneurysm of the aorta and innominate artery and dilatation of the esophagus cause mediastinal enlargement, they will not be considered in this discussion except to emphasize that retrograde angiography and roentgenkymography are helpful in diagnosing such vascular abnormalities and a barium swallow should establish the diagnosis of any esophageal pathology

In the paragraphs to follow, no attempt will be made to discuss each type of primary tumor separately Instead, the symptomatology, roentgenological findings and the clinical approach to diagnosis will be emphasized

Symptomatology

Frequently mediastinal tumors, even those of large size, are silent When symptoms are present, they are usually due to pressure, invasion or irritation of the various structures within or adjacent to the mediastinum It is apparent that the position of the tumor, as well as its size, rate of growth and pathological nature will determine its symptomatology

Respiratory Symptoms

Cough is one of the most common symptoms of a mediastinal tumor d is caused by involvement of the trachea and bronchi The same chanism may cause stridor, dyspnea orthopnea and cyanosis Vas- ar compression also contributes to the production of dyspnea and nosis

Symptoms Secondary to Nerve Involvement

Phrenic nerve—hiccough and diaphragmatic paralysis
Recurrent laryngeal nerve—hoarseness
Vagus nerve—slow pulse, vomiting
Sympathetic nerves—HORNER'S SYNDROME, unilateral sweating and flushing of face, cardiac irregularities, anginal attacks
Brachial plexus—pain down the arm
Intercostal nerves—pain or paraesthesias along the course of the nerve

Gastro-Intestinal Symptoms

Dysphagia is usually due to involvement of the esophagus itself

Pain

This can vary from a vague sense of substernal discomfort or pressure to a more severe type of pain secondary to involvement of bone, intercostal nerve or pleura

Vascular Symptoms

Obstruction of the superior vena cava is commonly due to tumor but may also be caused by thrombosis, fibrous mediastinitis and aneurysm The characteristic symptoms are edema, cyanosis and dilated veins of the face, neck, arms and upper thorax The associated cerebral conges-

tion causes vertigo, headache, tinnitus and, at times, unconsciousness At first these symptoms may be noticed only after exertion and stooping If the superior vena cava is occluded above the azygos vein, the dilatation of the superficial veins will be above the midthorax, the collateral circulation taking place through the external jugular, internal mammary and intercostal veins If the occlusion is below the azygos, the veins over the abdomen, back and groin will also become dilated because the blood must then return to the heart by way of the inferior vena cava

Obstruction of the Azygos or Pulmonary Veins

This may cause hydrothorax

Obstruction to the Thoracic Duct

This may cause chylothorax

Specific Symptoms

TERATOID TUMORS

At times one of these may rupture into a bronchus producing in the sputum such tumor contents as cholesterin crystals, fat droplets and hair The cyst then becomes infected and may simulate the clinical picture of empyema with fistula Violent paroxysms of coughing may be caused by the intermittent spilling of secretions into the bronchial tree

BRONCHIAL CYST

These also may rupture into the bronchi and simulate empyema with fistula

Systemic Symptoms

Benign mediastinal tumors are rarely associated with any systemic response When such symptoms as anemia, fever and loss of weight and strength are present, they are *usually the result of malignant changes* However, as Heuer and Andrus have pointed out, even in the presence *of malignant changes these symptoms are less frequently seen* than with other malignant tumors, probably because death occurs earlier from *compression symptoms*

Summary

Mediastinal tumors frequently produce no symptoms At other times the symptoms are slight and vague If left untreated, the majority of tumors will progress to cause serious symptoms which will depend upon the pathological nature and position of the tumor in the mediastinum Physical signs may be absent If present, they rarely serve as a guide to the type or extent of pathology The symptoms and signs associated with

mediastinal tumor are, therefore, vague and non specific. Usually they do nothing more than indicate the presence of the tumor

Roentgenological Aspects

The importance of over exposed x rays and multiple projections has previously been indicated Also, fluoroscopic study is important to study the dynamics of the tumor, especially whether or not it moves with swallowing or its margins show expansile pulsations It must be re membered that tumors adjacent to the aorta frequently appear to exhibit expansile pulsation and that aneurysms frequently do not Attention is again called to the fact that the mediastinal shadow changes with posi tion and the various phases of respiration This is an important considera tion when interpreting the films of a child, especially when enlargement of the thymus gland is suspected since the normal thymus appears en larged during expiration and crying Tracheal compression seen in the lateral view is required in addition to mediastinal widening to make a diagnosis of thymic enlargement in an infant

Once a tumor of the mediastinum has been demonstrated and a primary tumor suspected the following four lesions must be ruled out

(1) *Dilated Esophagus* This is ruled out by barium swallow

(2) *Aneurysms of Aorta and Innominate Artery* Aneurysm of the aorta may be located anywhere but is most common in the region of the arch It can frequently be distinguished by its expansile pulsations and its continuity with the aorta Roentgenkymography may be helpful, but if there is any doubt, retrograde angiography with 70 per cent dio drast should be performed Aneurysm of the innominate artery presents to the right side of the superior mediastinum. It often presents a difficult problem in diagnosis At time it may even move with swallowing If there is any suspicion concerning a tumor in this area, retrograde angio graphy should be carried out prior to any operative procedure

(3) *Paravertebral Abscess* This can easily be recognized by its in timate relation to the spine and the fusiform, bilateral, usually sym metrical shadow it casts on the over exposed postero anterior roentgeno- grams

(4) *The Lymphoblastoma* These are usually located in the middle mediastinum They may be unilateral but more frequently are bilateral The density is usually lobulated on its lateral border and continuous with the mediastinal shadow medially When the lymph nodes are involved bilaterally, there is little difficulty in differential diagnosis However,

when unilateral, a correct diagnosis may be impossible without a test dose of x-ray therapy. The lymphoma is radio-sensitive and should reduce in size following x ray therapy within seven to fourteen days (see Fig 1) The primary mediastinal tumors do not respond to x ray. If any superficial lymph nodes are involved, a biopsy will prove the diagnosis

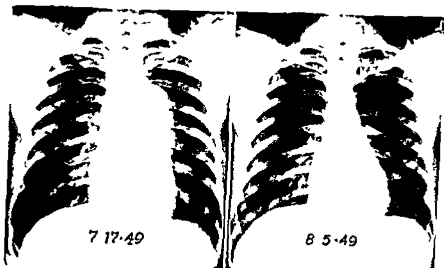


Fig 1A The roentgenogram prior to irradiation
Fig 1B The roentgenogram 19 days later showing the prompt and marked response to irridation
Mr P D—Age 29 Patient had no pulmonary symptoms *His* only complaint was weakness He had a marked anemia A diagnosis of lymphoma was established on the basis of roentgenological findings—a bilateral lobulated mediastinal mass and *enlarged paratracheal nodes on the right A pathological diagnosis of malignant* lymphocytoma was made by biopsy of one of the slightly enlarged cervical nodes In spite of the good response to x ray therapy, the patient's condition became *progressively worse and he died one month later, on September 8* 1949

Having ruled out these four conditions, the next step *is to attempt* to *identify the nature of the tumor in question by determining first its location and, secondly, whether or not it manifests any special characteristics It must be remembered that these are* helpful guides in diagnosis, but are *not to be considered infallible*

A. Location

1 Superior Mediastinum

The most common tumors *in this region are substernal goiters,* neurogenic tumors, *thymic tumors and bronchogenic cysts* The goiters and *tumors of the thymus* are usually anterior and bilateral and the neuro-

genic tumors posterior and unilateral The superior mediastinum is so small that frequently it is difficult to accurately determine the site of origin of the tumor True intrathoracic goiters, in contrast to the sub sternal type, may lie anywhere in the mediastinum

2 ANTERIOR MEDIASTINUM

The characteristic tumor of this region is the teratoid tumor (dermoid cyst, teratoma) Some lymphoblastomas lie here also

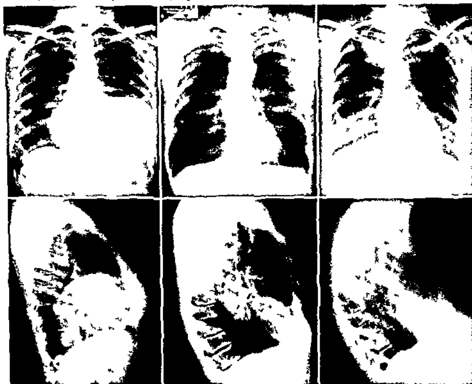


Fig 2A Teratoma PA and lateral roentgenograms reveal a large mass in the lower portion of the left chest Although this tumor lies predominantly in the anterior and middle mediastinum it is so large that it is difficult to determine its site of origin
Fig 2B Bronchogenic Cyst The PA roentgenogram shows a tumor mass situated near the midline so that its margins which are smooth and sharply delimited present on both sides of the sternum
The lateral view shows the cyst to be located in the middle mediastinum.
Fig 2C Neurofibroma The PA roentgenogram demonstrates a smooth rounded tumor mass to the right of the superior mediastinum
The lateral view shows that the tumor lies in the paravertebral gutter—a very typical location for the neurogenic tumor *Comment* All three of these mediastinal tumors were discovered by chest survey roentgenograms at a time when they were producing no symptoms

3 Middle Mediastinum

The lymphoblastomas are the most common tumors in this location Although the authors realize that bronchogenic cysts may be located anywhere in the mediastinum, we have been impressed by the fact that they usually fail to occupy the extreme *anterior position typical of the* teratoid group or the extreme posterior (paravertebral) position so characteristic of the neurogenic tumor They commonly lie in the approximate region of the middle mediastinum

4 Posterior Mediastinum

The neurogenic tumors are the characteristic group in the posterior mediastinum In fact, in the lateral roentgenogram they usually occupy the paravertebral region which actually lies posterior to the anatomical posterior mediastinum which is limited by the vertebral bodies

5 Tumors Lying in the Midline

According to Rigler, bronchogenic cysts, gastric cysts, and thymomas tend to lie in the midline and require careful lateral views for demonstration on occasion

B Special Characteristics

1 Unilateral Tumors

The teratoid and neurogenic tumors are usually unilateral The teratoma may present on both sides of the sternum when large

2 Bilateral Tumors

Fibromas, thymomas and enlarged thyroids are usually seen on both sides of the sternum

3 Calcification, Teeth and Bones

Not infrequently, calcification is seen in teratoid tumors Rarely, a *mediastinal* cyst will become calcified Teeth and bone may be seen in the teratoid tumors

4 Bone Erosion

Erosion of the vertebral pedicles is most commonly seen in neurogenic tumors *This finding always indicates the possibility of a* dumb bell type tumor lying partly in the thoracic cavity and partly in the vertebral canal However, mediastinal meningoceles are also associated with such defects and are apt to be multiple *Under such circumstances* myelography with air or iodized oil should be performed as it will readily *demonstrate the meningocele*

5 Lipoma

Mediastinal lipomas frequently show a peripheral zone of relative radiolucency around a more dense central zone Some lipomas are en

tirely intrathoracic Others are of the dumbbell type with both an intra and extrathoracic portion, the tumor protruding from the mediastinum either through an intercostal space or through the superior aperture of the thorax.

6 CHARACTERISTICS OF THE MARGINS OF TUMOR

Most of the benign tumors have a sharply delimited border When the border becomes hazy and ill-defined, malignant degeneration should be suspected The cysts usually have a very smooth margin The teratoma is apt to be lobulated

7 MOTION OF THE TUMOR WITH SWALLOWING

The substernal thyroids usually move with swallowing At times, this is true with bronchogenic cysts due to their attachment to the tracheobronchial tree Again, it is pointed out that an aneurysm of the innominate artery may also move with swallowing

The use of the above generalizations regarding the location and characteristics of mediastinal tumors provides a fairly accurate guide to diagnosis For instance, if one is dealing with a sharply circumscribed tumor mass in the paravertebral region it is probably a neurogenic tumor Should the vertebral pedicles be eroded, the diagnosis would be even more certain and an intraspinal extension of the tumor should be suspected On the other hand, if the tumor is in the anterior mediastinum with similar characteristics, it is probably a teratoid tumor If the tumor contains calcium, bone or teeth, this adds support to the diagnosis Likewise, a superior mediastinal tumor that tends to lie anteriorly, is bilateral, moves with swallowing and causes tracheal deviation is most certainly a substernal goiter A bilateral lobulated mass continuous with the mediastinal shadow and located in the middle mediastinum is probably a lymphoblastoma Thus, these facts can be pieced together in any given case and the result will be a fairly accurate diagnosis In any event, once the diagnosis of a primary mediastinal tumor has been established, it should be removed and the pathologist should decide not only what it is, but whether it is benign or malignant

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CHAPTER XXI

DISEASES OF THE OESOPHAGUS

By WILLIAM A HUDSON, M D

Anatomical and General Considerations

THE OESOPHAGUS is that portion of the alimentary canal which begins at the distal end of the pharynx and extends to the cardiac end of the stomach, beginning opposite the lower border of the cricoid cartilage or about the level of the 6th cervical vertebra and passing through the diaphragm at the level of the 10th or 11th thoracic vertebra The average length of the oesophagus in adults is about 25 cm The arrangement of its component tissues, its relationship to the various important structures of similar embryonal origin and those of close anatomical location have been factors of great importance in the development of diagnostic and therapeutic procedures applicable in the diagnosis and treatment of abnormalities and diseases of the oesophagus.

The walls of the oesophagus consist of three layers 1) the inner mucous membrane, 2) the loose submucosal coat, and 3) the outer muscular coat consisting of inner circular and outer longitudinal muscle fibers The cervical and thoracic portions of the oesophagus are imbedded in loose areolar tissue while the abdominal portion is invested with a layer of peritoneum

The mucosa of the oesophagus varies in color from a reddish color above to a pinkish gray in its distal portion and presents deep longitudinal folds The musculature is comparatively thick except in its proximal portion The muscle is arranged in two distinct layers of about equal thickness The inner layer of muscle fibers is circular and is continuous with the inferior constrictor proximally and the oblique fibers of the stomach distally The outer layer of muscle fibers is longitudinal It commences proximally as three flattened bands, a strong anterior band arising back of the cricoid cartilage and, two lateral bands blending with the stylopharyngeus and pharyngopalatine, all uniting to form

one layer which becomes continuous with *the muscular coat of the* stomach

The proximal one third of the oesophagus contains cross striated muscle fibers while the middle portion contains mixed smooth and *cross straited muscle* fibers and the third contains all smooth muscle fibers Occasional muscle bundles pass from the oesophagus to the mediastinal pleura and also to the posterior wall of the left bronchus

The blood supply of the oesophagus is derived from the inferior thyroid artery, the bronchial arteries, the oesophageal branches of the aorta, the intercostal arteries, the inferior phrenic, the gastric arteries and the left hepatic arteries and, *more rarely*, from the splenic and celiac arteries The arterial supply to the three segments of the oesophagus is, in general, segmental in nature The veins accompany the arteries forming a venous plexus on the outer surface of the oesophagus, they empty into the gastric coronary vein distally and the azygos and thyroid veins proximally, thus establishing a communication between the portal and systemic veins

The submucosa contains mucous glands, racemose in type, like the glands of the mouth In the lamina propria are found glands similar to those in the fundus of the stomach These glands are found at about the level of the 5th tracheal ring and also, near the cardiac end of the oesophagus Numerous lymphatics arise from the submucosa to drain into the lower cervical, posterior mediastinal and superior gastric nodes The nerve supply arises from the sympathetics and the vagus nerves

At the level of the cricoid cartilage, the oesophagus lies immediately in front of the vertebrae The trachea and part of the left lobe of the thyroid are largely anterior to the oesophagus and the recurrent laryngeal nerves and the carotid arteries and jugular veins are in close proximity on either side (right and left) in the cervical region The oesophagus deviates to the left so that the distal portion of the cervical oesophagus lies to the left of the trachea The thoracic oesophagus lies at first in the superior mediastinum anterior to the vertebrae deviating to the left to lie posterior to the origin of the left bronchus, with the left carotid and subclavian arteries, the corresponding veins, the arch of the aorta, the left recurrent laryngeal nerve and the left mediastinal pleura in close relationship, anterior and to the left The right vagus nerve, the thoracic duct and the right mediastinal pleura are in relationship on the right As the oesophagus passes from the superior to the posterior mediastinum it is in relationship to the posterior pericardium

and the descending aorta which lie almost parallel and to the left, the left vagus nerve lying anterior and the right vagus, posteriorly The oesophagus gradually passes toward the left and downward to cross in front of the aorta, thence, passing through the hiatus of the diaphragm In the posterior mediastinum, the oesophagus lies anterior to the hemiazygos veins, the right intercostal arteries, the thoracic duct and descending aorta The right mediastinal pleura, the azygos vein and the throacic duct lie to the right The descending aorta, the left mediastinal pleura are in relationship on the left The oseophagus is surrounded by the oesophageal plexus

The abdominal portion is short about 2 cm with the left lobe of the liver lying anterior and the left lobe of the liver and fundus of the stomach lying to the left The caudate lobe of the liver and posterior decussation fibers of the crura of the diaphragm and the left phrenic nerve lie to the right

The important points in the anatomic features of the oesophagus are

(1) It is a collapsible tube with a well developed mucosa and muscularis

(2) There is a poor adventitia with no well developed covering like the peritoneum or pleura

(3) The oesophagus is in close relationship to a number of vital organs

(4) The blood supply is derived from several sources

(5) There are variations in its caliber The narrowest points are

(a) At the level of the cricopharyngeal region

(b) Near the bifurcation of the trachea

(c) At the hiatus diaphragmaticus

Movements of the Oesophagus

The movements of the oesophagus can be divided into two groups

(1) The extrinsic which are transmitted movements They are brought about by two factors

(a) Respiratory movements which consist in an opening of the lumen of the thoracic oesophagus during inspiration This is due to the increase in negative tension within the thorax during inspiration

(b) Pulsatory movements due to pulsatile pressure of the

aorta at about 24 cm from the teeth and of the heart at about 30 cm from the teeth

(2) The *intrinsic movements* which are involuntary in nature

(a) Deglutition

(b) Regurgitation

(c) Spasmodic, which is usually associated with some pathological process

(d) Tonic, such as the closure of the cricopharyngeal and the hiatal diaphragmatic aperture

General Management

Aphasia, dysphagia, odynophagia or persistent abnormal sensation or disturbance of function of the oesophagus should command our immediate interest and study A painstaking history in regards to the character and onset of the symptoms, their variation in severity and distribution will aid in arriving at an early impression as to their cause Orderly approach to the study of oesophageal lesions is the best way to prepare oneself to meet the problems at hand or to anticipate and fore arm oneself to meet the complications which may arise I have never encountered an incident which justified one in throwing caution to the wind and rushing into some ill planned program for the treatment of an oesophageal lesion There are certain occasions of urgency, such as rupture of the oesophagus or the obstruction of the oesophagus by a very large object with tracheal compression which require immediate action to save a life Even on such occasions a routine program pre viously worked out will operate to the advantage of the patient

Symptoms

The similarity of the symptoms which one encounters in the various diseases of the oesophagus may be very confusing This similarity of symptoms is a challenge to the diagnostician to sort out the symptoms as regards their onset in relationship to each other and to the duration of the illness The historical study together with the observation of physical phenomena, i e, nutrition, the drooling of saliva cyanosis distention of veins of the upper chest and neck and other signs will give one a good idea as to the general location and character of the lesion and as to the laboratory procedures best suited for their further study

Pain and difficulty on swallowing are cardinal symptoms of oesopha geal disease Variations in the mode of onset, duration and extent of the

inconvenience or disability caused by the numerous diseases which may affect the oesophagus may be confusing at first sight It should be borne in mind that all complaints such as soreness, gurgling sounds and sensation of something being lodged in the throat on swallowing and regurgitation of food all fall in the category of difficulty in swallowing All such complaints should lead one to give careful thought and study to the condition of the oesophagus

It is recognized that many people experience the sensation of having something lodge in their throat while eating fish and other food In a considerable percentage of these cases the object is arrested momentarily in the pharynx or oesophagus only to pass on without inflicting more than temporary discomfort This knowledge should not lead one to disregard the fact that many objects including fishbones and tooth picks do lodge and perforate the wall of the oesophagus thereby exposing the patient to the danger of periesophageal or mediastinal infection and its most serious consequences

Symptoms of Oesophageal Disease

(1) Pain in neck or along sternal area in foreign body

(2) Substernal discomfort may be described as a pain or as a pressure fullness

(3) Difficulty in swallowing food lodges momentarily or for longer periods

(4) Regurgitation may occur soon after eating or at a stated period

(5) Regurgitation or vomiting of blood

(6) Gurgling sounds on swallowing or on palpation

(7) Subcutaneous emphysema (perforation of oesophagus or with flap like tear of mucous membrane)

(8) Loss of weight

(9) Respiratory distress compression of trachea or bronchi by foreign body or tumors

(10) Hoarseness pressure on the recurrent laryngeal nerve or extension of carcinoma to involve larynx and recurrent laryngeal nerve

(11) Difficulty in swallowing due to lack of muscular coordination (palatal paralysis congenital or acquired and defects in palate)

(12) Pain from laryngeal tuberculosis may cause difficulty in swallowing

(13) Constant desire to swallow or expectorate saliva

(14) Coughing after one or two draughts of liquids, high obstruction

(15) Foul breath

(16) Mass in neck reduced in size after regurgitation

Diagnostic Procedures

A patient who has been discomforted to such an extent that he comes for advice or relief should not be sent away until after a careful study has been made A careful history and a general physical examination with particular attention to the condition of the nose, mouth throat, pharynx, larynx and pyriform sinuses should be carried out Blood counts and urinalysis are routine examinations that should never be omitted A preliminary fluoroscopic study should be made This should include all parts from the head to the pelvis It is desirable, as a rule, to obtain postero anterior and lateral x ray films of the involved parts Additional fluoroscopic and radiographic studies, using contrast media, may be desirable The contrast media more commonly used are liquid barium, barium capsules and iodized oil The particular medium, the time and method of its use should be determined in each individual case according to the indications at the time of the study Metallic objects are, as a rule readily demonstrated in posterio anterior and lateral films This combination of studies afford the best opportunity for one to observe variations in the contour and function of the parts under investigation Frequently, such variations are the best clue to the site and character of the disease or abnormal condition present X ray studies, with some sort of a film record, are most desirable in all cases The films serve as a permanent record for future reference and they are valuable protection for the doctor from a medico legal standpoint

Oesophagoscopy, for confirmation of the findings demonstrated in the previous investigation, may be the means of finally establishing a diagnosis Direct inspection of the oesophagus, with the opportunity to obtain tissue specimens for microscopic examination, is of inestimable value In the management of oesophageal lesions, oesophagoscopy is of diagnostic and therapeutic value

The potential seriousness of all oesophageal lesions and their complications make it imperative that an accurate diagnosis be made and that forethought and deliberation be exercised in the choice of therapeutic agencies and measures Many oesophageal lesions were diag

nosed correctly and were treated with success previous to the introduction of x ray and oesophagoscopy, however, the proper use of the x ray and the oesophagoscope has led to more accurate diagnosis and more successful treatment of more oesophageal lesions than was possible previous to their introduction It is my firm conviction that, with the rarest exception no man is justified in proceeding with any form of instrumentation of the oesophagus without proper x ray studies having been made previous to such instrumentation

Diseases

Oesophagitis

Inflammation of the oesophagus is not uncommon and is characterized by variable degrees of redness and swelling of the mucous membrane with loss of vascular markings Oedema may be so great as to produce folds of the mucous membrane and diminution in the lumen of the oesophagus Acute inflammation may result from extension of pharyngeal or laryngeal infection into the oesophagus The submucosa may be involved and suppuration may result Successful treatment of such lesions can be accomplished best through the control of the primary infection

Tuberculous oesophagitis is usually a complication or an extension of laryngeal tuberculosis and may be characterized by ulceration and bleeding Swallowing of food may be painful with consequent loss of weight Tuberculous oesophagitis can be treated best by the same hygenic measures antibiotics and chemotherapeutic agents that have been found to be effective in the treatment of laryngeal and other tuberculous infections i e, rest therapy, acceptable food, streptomycin, PAS isonicotinic acid hydrazide and their companion agents

Inflammation of the oesophagus from actinomycosis and other fungi occurs infrequently The diagnosis of such lesions is made through the identification of the fungus involved Such lesions are best treated through the use of drugs enumerated in the chapter on Pulmonary Mycoses

Oesophagitis complicating typhoid fever is much less frequent today than formerly Typhoid fever is best controlled through preventive measures good sanitation, typhoid vaccines and chloromycetin

Diphtheria of the oesophagus is also rare since the process of immunization has reduced the incidence of diphtheria Its diagnosis can be made through the identification of the diphtheria organism in

smears and cultures from the lesions Treatment is outlined in the section on Diphtheria of the Lower Respiratory Tract

Esophagitis due to chemical irritation, iodine, lye, acid and other corrosive agents is readily recognized through the history of the patient having ingested such an agent and the usual excoriation of the buccal mucous membranes by the agent The immediate treatment of such lesions should be carried out with the utmost gentleness using a neutralizing agent at once

One may use weak acetic acid or mild alkali in the case of alkali or acid burns and starch water for iodine burns The use of penicillin and chemotherapeutic agents to control the infection will help to reduce the amount of scar which developes in the process of healing I am certain that ulceration will be less extensive and that active dilatation of the oesophagus can be initiated within the first week in many instances, thereby lessening the dangers of complete stenosis The causal agent or disease must be treated in all cases of stricture of oesophagus The narrowing of the oesophagus which results from the scar formed in the process of healing must be dealt with by gentle and careful dilatation

One should be careful that he does not overlook evidence of any of the agents having entered the airway, larynx or trachea If the larynx is obstructed proper provision should be made to maintain ample air way Tracheotomy may be life saving The oesophageal lesion is to be treated by the use of sterile olive oil the early but careful passing of an oesophagoscope of proper size (not too large) for the aspiration of secretions and to prevent synapsis of the oesophageal walls Dilatation of the oesophagus should be done regularly, once or twice weekly, to prevent contracting scars from obstructing the oesophagus Fluids can be administered by vein if sufficient fluids cannot be taken by mouth The use of penicillin and sulfa drugs lessens the danger of complete occlusion of the oesophagus by contracting scars

Chronic inflammation of the oesophagus is usually associated with and results from the prolonged presence of foreign material foreign bodies food or secretion in the oesophagus The symptoms are usually those of discomfort or a dull ache referred to the ribs the sternal region or into the back, with variable degrees of difficulty in swallowing Treatment consists of removal or correction of the cause of the retention of foreign material food or secretion and then use of penicillin and sulfa drugs Any strictures resulting from such lesions

should be treated by oesophagoscopy and dilatation of the stricture.

OESOPHAGEAL ULCERS

Ulcers of the oesophagus may be accompanied by pain on swallowing, if the ulcer is in the upper one third of the oesophagus there may be regurgitation of blood and difficulty in swallowing An ulcer may be encountered in the presence of foreign body of long residence in the oesophagus

Tuberculous ulcers are usually associated with tuberculous laryngitis and pulmonary tuberculosis and should be treated with streptomycin at the same time the pulmonary or laryngeal lesions are being treated

Syphilitic ulcers of the oesophagus are not frequent but such lesions should be proven by serological and microscopic studies Treatment is the same as for systemic syphilis In addition, those cases developing cicatricial obstruction should be subjected to dilatation or resection as may be indicated

Peptic ulcers usually occur in the lower one third of the oesophagus and are accompanied by dull, boring pain that extends into the back X ray studies may fail to demonstrate the ulcer Oesophagoscopy with biopsy gives the most convincing proof of the nature of the lesion Treatment is the same as for gastric ulcer but resection of the ulcer bearing portion of the oesophagus with a portion of the stomach may be necessary

Chronic nonspecific granulomata of the oesophagus have been described and are characterized by the symptoms of obstruction They may be mistaken for carcinoma of the oesophagus except for the fact that the microscopic sections do not reveal evidence of cancer Some of these lesions may be due to the ingestion of foreign bodies which are forgotten Others may be secondary to local lesions within the mediastinum but there is the occasional case for which no explanation can be discovered Some cases respond to dilatation with bougie, others may become completely obstructed in spite of the measures applied and require resection of the involved portion of the oesophagus or an oesophagoplasty

Ulcerations accompanying malignancies and other tumors are best treated by treating the neoplasm (See discussion on carcinoma)

STRICTURES OF THE OESOPHAGUS

A stricture is defined as a localized, morbid narrowing of any passage of the body The most common cause of the development of

cicatricial stenosis of the oesophagus is the ingestion of caustics or acids either accidentally or by intent, the other factors which may cause narrowing or stricture of the oesophagus are noted in the outline and none must be disregarded The cause of such stenosis is usually ascertained from the history Two *important features in the treatment* of any stricture are (1) ascertain and remove the cause, and (2) re establish the passageway

A discussion of stricture of the oesophagus, if approached from its broad aspect, would include those localized narrowing of the oesophagus which are *intrinsic arising in the oesophageal wall and those that are* extrinsic or arising from without the wall of the oesophagus

Intrinsic (obstruction) stricture may be

(1) *Congenital or developmental in origin (see discussion)*
(2) Corrosive from the swallowing of caustic acids or alkalies
(3) Cicatricial resulting from the processes of healing of peptic ulcers, diphtheritic, syphilitic, tuberculous or nonspecific oesophagitis
(4) Healing of burns and scalds from ingestion of hot foods or other substances
(5) Neurogenic disturbances (see discussion of Cardiospasm)
(6) Neoplastic tumors including carcinoma and polyps

Extrinsic or compress on stenosis may be due to

(1) Enlargement of mediastinal lymph nodes
(2) Aneurysm
(3) Spinal deformity with oesophageal distortion
(4) Compression or distortion by enlargement of the thyroid or tumors of the thyroid
(5) Mediastinal tumors
(6) Pericarditis or pleuritis adhesive or with effusion

Strictures are most frequently multiple occurring at

(a) The crossing of the left bronchus
(b) Near the cricopharyngeal region
(c) The hiatus level

Symptoms and local changes associated with stricture or oesophageal obstruction

Dysphagia

Regurgitation and a *sense of fullness or distress after* eating with loss of weight may be *encountered in association* with stricture of the oesophagus Complete obstruction may result from the lodging of par

ticles of food at a narrow point (green peas, corn and other vegetables or meat may be the offending article) The stenotic area is usually pale and the scar may be very white, there may be retraction of mucosal surface or it may be level with adjacent surface or even raised (keloid) The point of narrowing may be annular, usually is excentric and, at times, there is pouching of the mucous membrane, retention and stagnation of food in such areas may result in erosion and ulceration with bleeding

Strictures due to burns with acids or other chemicals should be treated by dilatation under direct vision through the oesophagoscope using graded bougies at intervals varying from once or twice a week to once in a month or longer depending upon the severity of the obstruction and upon the response to treatment The end result and the functional satisfaction will depend upon

(1) Extent and density of the scar

(2) Persistence and gentleness in application of the various procedures

One must never loose sight of the danger of perforation of the oesophageal wall while passing any instrument Such calamities have happened to the most experienced men but they occur most frequently with the less experienced and especially during blind bouginage Most perforations occur either at attempts to pass an instrument through the narrow points such as the cricopharyngeal region or cardia or during the removal of foreign bodies Blind bouginage is never to be countenanced In case of perforation, immediate mediastinotomy with repair and continuous drainage and antibiotic and chemotherapeutic measures are most urgent

Oesophagoscopy with sawing of webs with a string is dangerous The danger of the spread of infection throughout the mediastinum is too great Areas of extensive scarring can be treated more safely by resection of the scarred portion of the oesophagus and the reestablishment of the continuity of the passage by uniting the proximal and the distal ends of the cut oesophagus or by uniting the proximal end of the oesophagus with the stomach

PERFORATION OF THE OESOPHAGUS

Perforation of the oesophagus at instrumentation or through other accidents is followed by mediastinitis and may result in death unless bold measures are instituted Perforation of the subclavian artery with fatal hemorrhage into pleural space has occurred Oesophago-

tomy is less hazardous today than formerly because of the improved techniques, the use of chemotherapeutic agents, penicillin, etc These agents enable us to combat infection and to secure early healing which was not formerly possible Large objects and many pointed objects may now be removed more safely by oesophagotomy than by other means A majority of foreign bodies can be removed at oesophagoscopy with properly selected oesophagoscope as regards size of tube and with forceps suitable for grasping an object of the type to be removed Extreme care must be exercised that the object is withdrawn without adding to the damage already caused by the object

CONGENITAL ATRESIA OF THE OESOPHAGUS

The term atresia is defined by Webster as " not perforated' or ' absence or closure of a natural passage or channel of the body The condition with which we are concerned at this time is that of an abnormality of the oesophagus which is present at birth The most common abnormalities of this type are shown in the following diagrams

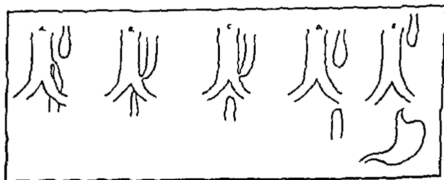


Fig 1 Illustrating various types of congenital abnormalities of the oesophagus

Diagram A illustrates the type most frequently encountered The symptoms are dyspnea and strangulation from saliva entering the air way or from aspiration of feedings These symptoms in any new born child should lead to a suspicion of such a defect The careful insertion of a catheter with x ray films as a record should give ample evidence of a blind pouch Some advocate the use of iodized oil as a contrast medium Immediate surgical procedures should be instituted Delay invites the further aspiration of secretion into the airways with tracheobronchial and pulmonary infection thereby, reducing the chances of a successful outcome The procedure of choice is to establish a passage way from the mouth to the stomach by uniting the two segments of the

oesophagus through an end to end anastomosis Any communication with the airway must be closed The absence of sufficient oesophageal tissues to permit the approximation of the two ends of the oesophagus makes it necessary to resort to other means of establishing a passageway A number of procedures have been used with variable degrees of success Among the procedures that have enjoyed a degree of success are

1) The intrathoracic union of stomach or the jejunum with the proximal oesophageal stump
2) The formation of an extrathoracic oesophagus through the use of skin tubes or of the extrathoracic union of the stomach or jejunum with the proximal oesophagus

The numerous cases which have been treated successfully attest to the value of the chosen procedures for correction of this congenital defect

CARDIOSPASM

(Achalasia—idiopathic dilatation—phrenial spasm)

This term is applied to a clinical and pathological entity characterized by narrowing of the oesophageal passage at the diaphragmatic hiatus retention of food in the oesophagus with dilatation and redundancy of the oesophageal wall and with chronic oesophagitis There may be a feeling of fullness or pressure within the mediastinum with actual soreness Eructation of gas and regurgitation of food are common symptoms The patient may empty large quantities of undigested food on lying flat or on stooping

The etiology of this condition is not fully known Jackson has described a pinch cock action of the crura of the diaphragm This dysfunction is associated with a disturbance in the action of the normal oesophageal mechanism In many patients the presence of a neurotic factor is noted and in some cases the passage of an oesophagoscope or the use of a hydrostatic or aerostatic dilator may suffice to relieve the symptoms Usually the proximal dilatation or widening of the lumen of the oesophagus does not disappear under such treatment Antispasmodics are used with a certain degree of success but one must not loose sight of the fact that periods of remission of the more severe symptoms occur without any treatment The longer the disease has been present the more difficult it is to relieve the symptoms. Those cases which are not relieved by medical measures and oesophageal dilatation may be relieved by surgical procedures Plastic operations of the type performed on the pylorus (Ramsted type) have given relief

in some cases It may be necessary to resect a segment of the oesophagus and reunite the oesophagus with the stomach On two occasions, I have divided bands of scar like tissue without disturbing the muscular or mucosa layers and the patients have had complete relief There is another valuable plastic operation which enlarges the lumen by incising *the full thickness of the oesophageal wall* into the lumen in the longitudinal plane Next, resuture of the incision so as to attach the proximal end of the incision to the distal end of the incision thereby leaving a transverse widening of the lumen at the point of closure, finally, one may resect a segment of the oesophagus and join the proximal end of the oesophagus to the stomach

It is my belief that the etiological factors involved in the early stages of the disease are, in all probability, much the same The lapse of time with the retention of food, the presence of infection, increasing inflammation and the development of scar tissue with the drag of the baggy *oesophagus as it swings into the* sulcus, aggrevate the *obstruction* thereby, causing the symptoms to increase in severity and to become *more persistent*

In the more severe cases surgical intervention is the procedure of choice

Hysterical Dysphagia

It is not uncommon for this diagnosis to be made but even in a patient who is known to be of an unusual nervous nature, care should be taken to study all aspects of the complaint before accepting a diagnosis of hysteria Too many foreign bodies, malignancies and other diseased conditions have been overlooked because someone failed to study the problem Should no evidence of oesophageal disease be *demonstrated* by the physical examination and x ray studies, oesophagoscopy should *be done, that by direct inspection of the oesophagus* no demonstrable disease or abnormality may be overlooked

Treatment

Treatment should be the same as in any other patient with hysteria On the other hand if a lesion is demonstrated, treatment should be that of choice for the lesion demonstrated

Diverticulum of the Oesophagus

A *diverticulum is a blind tube or sac branching off* from a cavity or canal Such blind sacs occur along the oesophagus The junction *of the oesophagus* and the pharynx is a site of predilection for the pulsion type of diverticulum The diverticula occurring at this site are

related to the anatomy of this part and are brought about by the relationship between the inferior constrictor muscle and the obliquely passing fibres of the cricopharyngeus as they descend upon the posterior wall of the oesophagus to become longitudinal fibres It is at this point that pulsion diverticula occur when there is incoordination in the function of these related muscles They appear first as a small bulge which soon becomes a sac As the sac enlarges, its course is downward and it becomes distended with food Its walls are composed largely of mucosa and submucosa With increasing size, the long axis of the sac comes to lie parallel with the long axis of the oesophagus The sac moves upward and downward in the neck on swallowing and, as it enlarges, enlargement is downward into the superior mediastinum

Instrumentation of the oesophagus, in the presence of a large sac, becomes hazardous because of the danger of perforation of the wall of the sac as the instrument is very likely to be passed directly into the sac and through its distal wall instead of down the main oesophageal channel

Diverticula of the oesophagus may be complicated by the presence of perioesophageal infection or by the presence of carcinoma in the sac The presence of blood in the mucus expelled from the sac should lead to suspicion of maligancy

The diagnosis of pulsion diverticulum can be made most certainly through the demonstration of the presence of a distinctive body, neck and aperture into the oesophagus through the use of contrast media at fluoroscopy and radiography It is important that both posterioanterior and lateral x ray films be taken, otherwise, a spherical dilatation of the oesophagus may be mistaken for a diverticulum Dilatations of this type occur in certain cases proximal to the scar of previous operations or strictures

The symptoms vary with the various stages of development In the early stages when the sac is a mere bulge, the only symptoms may be a feeling of fullness in the neck or the occasional lodging of a particle of food within the bulge This may result in a clearing of the throat or a hawking As the sac enlarges and more food is caught within it, unpredictable expulsion of food may occur, day or night The mixture of food and air within the sac may produce gurgling sounds upon swallowing or when pressure is placed upon the sac This sound may be audible to the patient s friends Finally, as the sac continues to enlarge, obstructive symptoms occur These are due to the fact that,

in the case of large sacs, the downward drag of the heavy sac causes the opening into the sac to be brought into alignment with the proximal oesophageal lumen so that food passes directly through the opening into the sac At the same time, the oesophageal passage is distorted in such a manner that food cannot pass down the oesophagus

TREATMENT

The treatment of pulsion diverticula is essentially surgical but during the period when the diverticulum has not produced major deformity of the oesophageal passage and while food will still pass down the oesophagus, dilatation may relieve the obstructive symptoms but does not materially delay the increase in size of the sac The danger of perforation of the sac through the passage of instruments must be kept in mind constantly

The surgical removal of the sac is the treatment of choice Operation should not be done during the early stage while the sac is a mere bulge The best time for operation is while the sac is small but has reached that stage when there are no inflammatory adhesions the aperture into the oesophagus is small and, there is a good neck to the sac

Two types of operation are commonly performed Some men prefer to dissect the sac free of its surrounding structures cut it away across the neck and suture the defect all in one operation Other men prefer to dissect the sac free of its surrounding structure implant it in the wound in an inverted position when possible or in the case of a large sac, to bring the sac out through the wound to lie upon the neck closing the wound, then later resect the sac and close the oesophageal opening with sutures

The advantage of the latter procedure or two stage operation is that in the large sacs the danger of infection in the tissues of the neck is greatly reduced through the sealing off of the fascial planes by the healing of the soft tissue wound Leaks which occur at the time the sac is cut away usually heal

Other procedures such as inversion of the sac and cutting it off with a snare through the oesophagoscope, twisting the neck of the sac and suturing in place have been used in treating pulsion diverticula but none are as free of complication or as satisfactory as either the single or two stage operation

TRACTION DIVERTICULA

Traction diverticula of the oesophagus are usually asymptomatic and rarely require treatment They occur along the full length of the

oesophagus but more commonly in the middle and distal one thirds of the oesophagus Should the sac grow to such a size that it causes symptoms, excision with careful repair of the oesophageal defect is the procedure of choice The antibiotics such as penicillin, streptomycin and sulfa drugs should be used freely in all surgery of the oesophagus to aid in the prevention and control of infection

HIATAL AND DIAPHRAGMATIC HERNIA

Hiatal herniation and diaphragmatic hernia may present symptoms of oesophageal obstruction A diagnosis can be established through a study of the history and the use of fluoroscopy and gastrointestinal x-ray studies Detailed discussion of this subject is presented in the chapter on Diseases of the Diaphragm

OESOPHAGEAL VARICES

Varices of the oesophagus develop as a compensatory mechanism to relieve portal hypertension Bleeding from oesophageal varices has been an alarming and even fatal symptom Varices of the oesophagus vary as to their size and in the extent of their distribution They may be demonstrated near the cardiac portion of the oesophagus or they may be distributed from the cardia to the cricopharyngeous level Barium studies of the oesophagus may demonstrate a worm like configuration at the site of the varices Direct inspection of the vessels at oesophagoscopy is an additional and valuable means of obtaining information Severe bleeding is a contraindication to oesophagoscopy

Control of hemorrhage from oesophageal varices is not always easy Many procedures have been used with variable degrees of satisfaction The injection of sclerosing solutions into oesophageal varices has been of value in chosen cases, omentopexy, portal caval anastomosis, splenic to renal vein anastomosis and total gastric resection have all been used in an attempt to reduce the portal hypertension Most of these procedures have afforded many failures Packing of the mediastinum has been carried out to create a bed of perioesophageal granulation tissue with an increased venous plexus to take some of the load from the varices, thereby reducing the pressure within the varices and lessening the danger of hemorrhage

This procedure may prove to hold considerable merit

Severe bleeding has been controlled for a time by balloon tamponage of the oesophagus The balloons are placed in the oesophagus and extend slightly into the stomach The balloons are inflated and left in place Aspiration of the stomach contents affords an opportunity to de-

termine if bleeding is stopped Once bleeding is controlled, there remains the problem of reducing the portal hypertension by one of the aforementioned procedures

CYSTS OF THE OESOPHAGUS

These are usually of congenital origin They may contain glands which produce secretions of gastric nature and may become very large The symptoms are due to pressure on adjacent organs and to complications especially those due to infection With compression of *the oesophagus, obstructive symptoms will be present* The method of treatment is operation

BENIGN TUMORS OF THE OESOPHAGUS

Benign tumors of the oesophagus occur infrequently, however, they constitute an important group because of the fact that they are curable The symptoms in this group of cases are similar to those encountered in any obstructive lesion of the oesophagus Dysphagia may not appear as early in the benign lesions as in carcinoma The roentgen ray studies with contrast media present the most characteristic indication of the benign character of the lesion This is evidenced by the elasticity of the oesophageal wall Unless there is ulceration, the outline of the tumor is, as a rule, smooth with a break in the continuity of the outline, appearing only at the upper margin of the negative shadow

These tumors lend themselves to surgical removal Reports are found *indicating the successful removal* of pedunculated tumors through the oesophagoscope with the use of a snare. Others have been removed successfully through surgical approach through the chest with the oesophagus *being opened and the tumor excised* The oesophagus is then repaired according to the fundamental rules for repair of this structure

Until recently the following types of tumors have been identified

Pathological Diagnosis	*Total*
Aberrant thyroid	1
Adenoma	3
Benign giant cell tumor	1
Cyst	6
Fibroma	8
Hemangioma	1
Leiomyoma	6
Lipoma	5
Lipomyoma	1
Myoma	10

Myxofibroma	1
Neurofibroma	1
Osteochondroma	9
Papilloma	35
Polyps	3
Unclassified benign tumor	
Total	91

DYSPHAGIA LUSORIA

This is a condition which is characterized by difficulty in swallowing There may be a feeling of fullness or stuffiness in the upper mid chest X ray studies reveal evidence of compression or notching of the oesophagus posteriorly at a level near the arch of the aorta At oesophagoscopy narrowing and transmitted pulsation are observed in the posterior wall of the oesophagus near or proximal to that produced anteriorly by the arch of the aorta

The anatomical relationships which operate to produce this dysphagia are of embryonal origin They are illustrated in the accompanying drawing which shows an anamolous right subclavian artery arising from the left portion of the aortic arch and passing posterior to the oesophagus The oesophagus is thereby caught between two large vessels Treatment has been symptomatic except that more recently the anomolous vessel has been sectioned that pressure against the oesophagus might be relieved

Other vascular anomolies such as double aortic arch which produce a vascular ring to encircle the oesophagus may produce dysphagia

CARCINOMA OF THE OESOPHAGUS

Carcinoma of the oesophagus is a devastating disease which occurs most frequently in men and women past mid life The most common site at which it occurs in order of frequency are middle third lower third and upper third at or near those natural points of narrowing in the oesophagus The incidence in the male and female varies in different series of cases but about 75 per cent of all carcinomata of the oesophagus occur in the male The distribution of the lesions in the oesophagus also varies but about 5 per cent of the lesions occur in the cervical oesophagus, 11 per cent in the upper third 42 4 per cent in the middle third and 38 8 per cent in the lower third Multiple lesions of the oesophagus have been reported There is little variation in the incidence in the white and colored races.

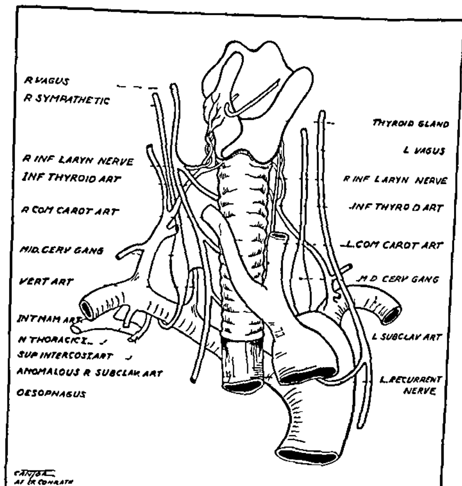


Fig 2 An example of an anomalous right subclavian artery passing posterior to the oesophagus with the aortic arch lying anterior the oesophagus being trapped between the two vessels

The tumors are classified histologically

		Per cent
1st	Epidermoid	56 6
2nd	Adenocarcinoma	17 2
3rd	Undifferentiated	4 9 with about 21 per cent unclassified

The squamous cell carcinoma may appear in any portion of the oesophagus while the adenocarcinoma appears in the distal portion of the oesophagus

The symptoms of the disease are the same as those encountered in any obstructive process The first symptom is usually that of a conscious

difficulty or interference with the act of swallowing. The severity of the difficulty is dependent upon the degree of oesophageal narrowing and may be greater or less from time to time depending upon the extent of local inflammation and swelling of the mucous membrane. The character of the food taken at any given time will influence the symptoms. Coarse foods may block the oesophagus at the point of narrowing and the patient may be unable to swallow until the food which blocks the passage has been removed or dislodged. Liquids will usually pass until obstruction is complete. Bleeding occurs as a later symptom and may be severe when ulceration has taken place or after trauma to an otherwise intact mucous membrane. With increasing obstruction, regurgitation or vomiting will sooner or later occur. Foul odor appears when food accumulates and undergoes putrefaction. Pain is a variable symptom, the pain may be dull, aching and in the back or substernal but, if the carcinoma should involve the intercostal nerves, pain may be severe and sharp and may radiate to distant areas. Weakness is a frequent symptom. Hoarseness is not uncommon and may result from the aspiration of food or liquid into the larynx and trachea from the pharynx or it may result from involvement of the recurrent laryngeal nerve by the carcinomatous process.

Cough and sputum accompanied by fever are late symptoms which may result from aspiration of food with accompanying pulmonary infection introduced through the foreign material in the airway or with the spilling of oesophageal contents through perforations into the airway. Such perforations usually occur late in the disease but are not uncommon.

Swelling of the neck with edema and congestion of the blood vessels of the upper part of the chest, shoulders, neck and head may be seen as a result of the obstruction of the superior vena cava by the carcinoma or through pressure produced by the involved regional lymph nodes.

Diagnosis of carcinoma of the oesophagus is dependent upon a careful study of the oesophagus by means of x ray with the use of contrast media barium being the one in common use. This should be followed by oesophagoscopic studies noting any deviation from normal in the appearance of the longitudinal folds of the mucous membrane. It is important to note any zones of fixation of the wall or deformity in the contour of the lumen of the oesophagus. Tissue for microscopic studies

should be obtained from any masses or areas of induration or ulceration

TREATMENT

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CHAPTER XXII

DISEASES OF THE PLEURA

By Louis L. Friedman, M.D.

General Considerations

Although the pleura is only a paper thin serous membrane, its anatomical size fails to reflect its real importance in health and disease. By virtue of its position and disease resistant properties, it may act as a barrier to the further spread of disease in the endothorax. Diseases of the pleura are very rarely primary. Since this discussion is limited to a consideration of the non tuberculous diseases of the pleura, the latter fact acquires added significance. With the exception of mesothelioma of the pleura, primary involvement by non tuberculous processes is indeed a rare occurrence. Because of its intimate relationship with the lung and other thoracic and upper abdominal structures, it is only too frequently secondarily involved by diseases of adjacent and neighboring organs. Certain generalized systemic illnesses also show an unusual predisposition for pleural involvement. Indeed, the pleura can fall heir to almost any disease which involves contiguous or distant tissues. In view of these facts, the need for a clear and concise classification of pleural diseases is imperative. Unfortunately, the large number of disease entities which involve the pleura, together with our very limited and meager knowledge of many, precludes the possibility of a satisfactory classification at the present time. For the sake of simplicity, pleural diseases will be classified in this presentation as inflammatory, mechanico-circulatory and neoplastic. This arbitrary division is based on morbid anatomy and etiology. Consequently, there is a considerable amount of unavoidable overlapping.

Anatomy and Physiology

The pleura closely invests the outer surface of the lungs and lines the endothorax. The part which invests the lung is known as the visceral

lysis of the exudate, therefore is not responsible for its removal Instead it is replaced from within outward by a layer of young vascular connective tissue This process is known as organization and occurs only in fibrinous exudates Recovery from the underlying disease process is usually followed by complete organization of the pleural exudate After replacement has been affected the pleura may appear perfectly normal and evidence of past inflammation can be ascertained only by microscopic examination of the membrane The recuperative properties of the pleura are truly amazing Many cases of pleuritis, unquestionably, are overlooked clinically and even after pathologic study In a significant number of cases, however permanent pleural and diaphragmatic adhesions may persist after replacement of the fibrinous exudate These are more frequent in the lower part of the endothorax in contradistinction to tuberculous adhesions which usually are found in the upper part of the thoracic cavity If the disease is progressive the fibrinous exudate may be replaced by a sero fibrinous effusion

SERO FIBRINOUS PLEURISY

The etiology of sero fibrinous exudates is similar to that of fibrinous pleuritis The amount of the effusion varies greatly and is dependent on the extent and nature of the disease process Usually the fluid is grossly clear and serous in nature Depending upon the fibrinogen content and other suspended material it may be light yellow milky or opalescent Its protein content predominantly fibrinogen is 4 per cent or more and its specific gravity is 1 018 or higher Because of its high fibrinogen content, it possesses the ability to clot As a rule clotting does not occur until the fluid is withdrawn from the thoracic cavity Occasionally when the fibrinogen content is very high fibrin balls (Fig 1) may form in the pleural cavity These are smooth regular round or oval shaped bodies of varying sizes which persist after the disease has subsided The cellular elements in pyogenic effusions are predominantly polymorphonuclears although other cells such as lymphocytes and eosinophiles may be present in varying numbers In non pyogenic exudates the number of lymphocytes are proportionately higher Eosinophile cells are present in unusually large numbers or actually predominate the cellular picture in certain effusions A reasonable explanation for this uncommon characteristic of pleural fluid is not always available Bacteria may be found on direct microscopic examination of an appropriately stained smear of the fluid but more frequently identification depends upon indicated cultural procedures

A substantial number of pyogenic effusions may yield sterile cultures consistently If a non pyogenic basis for the effusion is also lacking it is customary to attribute these so-called idiopathic effusions to a tuberculous origin Since the fibrinogen content of sero fibrinous exudates varies so widely in the same and different diseases it has be



Fig 1 Fibrin ball in right hemithorax following resorption of sero-fibrinous effusion

come the practice to classify the effusion as serous or sero fibrinous Clinically, however the terms are used interchangeably The differentiation has no real merit and is usually quite arbitrary

In this presentation all exudates which are not frankly purulent are considered sero-fibrinous The name sero fibrinous has pathological as well as clinical significance Further subdivision tends to confuse the issue and is actually without appreciable benefit Broken down cellular elements and proteins may be so suspended in a sero-fibrinous effusion as to impart a milky appearance to the exudate From gross inspection this type of exudate may be erroneously labelled as chylous but micro-

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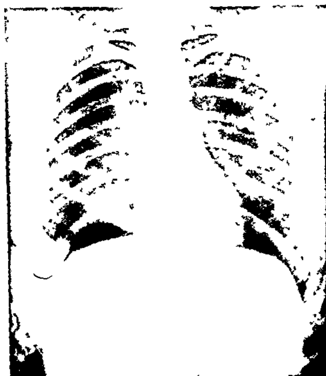


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lysis of the exudate, therefore, is not responsible for its removal Instead it is replaced from within outward by a layer of young vascular connective tissue This process is known as organization and occurs only in fibrinous exudates Recovery from the underlying disease process is usually followed by complete organization of the pleural exudate After replacement has been affected, the pleura may appear perfectly normal and evidence of past inflammation can be ascertained only by microscopic examination of the membrane The recuperative properties of the pleura are truly amazing Many cases of pleuritis unquestionably, are overlooked clinically and even after pathologic study In a significant number of cases however, permanent pleural and diaphragmatic adhesions may persist after replacement of the fibrinous exudate These are more frequent in the lower part of the endothorax in contradistinction to tuberculous adhesions which usually are found in the upper part of the thoracic cavity If the disease is progressive the fibrinous exudate may be replaced by a sero fibrinous effusion

SERO FIBRINOUS PLEURISY

The etiology of sero fibrinous exudates is similar to that of fibrinous pleuritis The amount of the effusion varies greatly and is dependent on the extent and nature of the disease process Usually the fluid is grossly clear and serous in nature Depending upon the fibrinogen content and other suspended material it may be light yellow milky or opalescent Its protein content, predominantly fibrinogen is 4 per cent or more and its specific gravity is 1 018 or higher Because of its high fibrinogen content it possesses the ability to clot As a rule clotting does not occur until the fluid is withdrawn from the thoracic cavity Occasionally, when the fibrinogen content is very high fibrin balls (Fig 1) may form in the pleural cavity These are smooth, regular round or oval shaped bodies of varying sizes which persist after the disease has subsided The cellular elements in pyogenic effusions are predominantly polymorphonuclears although other cells such as lymphocytes and eosinophiles may be present in varying numbers In non pyogenic exudates the number of lymphocytes are proportionately higher Eosinophile cells are present in unusually large numbers or actually predominate the cellular picture in certain effusions A reasonable explanation for this uncommon characteristic of pleural fluid is not always available Bacteria may be found on direct microscopic examination of an appropriately stained smear of the fluid but more frequently identification depends upon indicated cultural procedures

A substantial number of pyogenic effusions may yield sterile cultures consistently If a non pyogenic basis for the effusion is also lacking, it is customary to attribute these so called idiopathic effusions to a tuberculous origin Since the fibrinogen content of sero fibrinous exudates varies so widely in the same and different diseases it has be



Fig 1 Fibrin ball in right hemithorax following resorption of sero-fibrinous effusion

come the practice to classify the effusion as serous or sero-fibrinous Clinically, however the terms are used interchangeably The differentiation has no real merit and is usually quite arbitrary

In this presentation all exudates which are not frankly purulent are considered sero fibrinous The name sero fibrinous has pathological as well as clinical signifiance Further subdivision tends to confuse the issue and is actually without appreciable benefit Broken down cellular elements and proteins may be so suspended in a sero fibrinous effusion as to impart a milky appearance to the exudate From gross inspection this type of exudate may be erroneously labelled as chylous but micro

scopic examination, *proper staining, and chemical analysis of the fluid* will easily establish its true nature Such exudates are chyloid and not true chylous effusions Effusions of long duration may have a brownish discoloration probably due to the presence of cholesterol Very few cases of fibrinous pleurisy, whether treated or untreated, progress beyond the stage of sero fibrinous exudation After the sero fibrinous effusion has subsided, the pleura usually returns to a grossly normal appearance as previously indicated in the discussion of fibrinous pleurisy *The only evidence of previous inflammation may be the finding* of pleural adhesions at necropsy Obliteration of the costophrenic angle

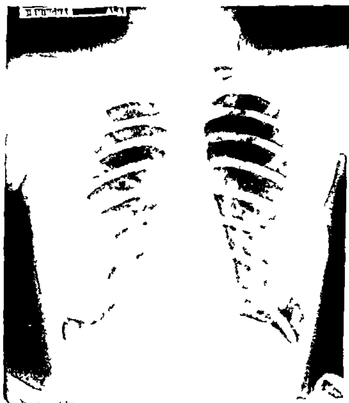


Fig 2 Blunting of right costophrenic angle following undiagnosed *sero-fibrinous* effusion

(Fig 2) tenting irregular flattening or elevation of the diaphragm (Figs 3 4) and thickened pleura in interlobar fissures are *frequently observed* in x ray films of the chest *Infrequently, fibrin* balls and generalized pleural thickening may be observed long after recovery from the

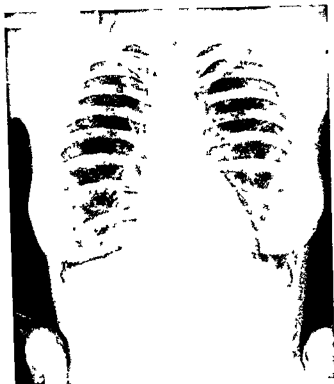


Fig 3 Bilateral blunting of costophrenic angles with tenting and irregular flattening of diaphragm History of bilateral pneumonia with pleurisy in childhood

original disease In contrast to its rather common occurrence following pyothorax, calcification of the pleura due to sero fibrinous pleurisy probably never occurs

EMPYEMA

A frankly purulent pleural exudate is known as empyema or pyothorax It is only rarely primary and, as a rule, is generally secondary to a suppurative disease of the lungs or other neighboring thoracic and upper abdominal organs Infections of the pleura without involvement of the underlying pulmonary tissue, if they ever occur, must be blood borne from a distant focus Sero fibrinous exudates only infrequently become frankly purulent Conversion of a sero fibrinous pleurisy to empyema, however, may follow diagnostic or therapeutic thoracentesis unless rigid sterile technique is observed Another important exception is streptococcal empyema which complicates epidemic influenza or measles The pleural reaction in this instance is at first sero fibrinous

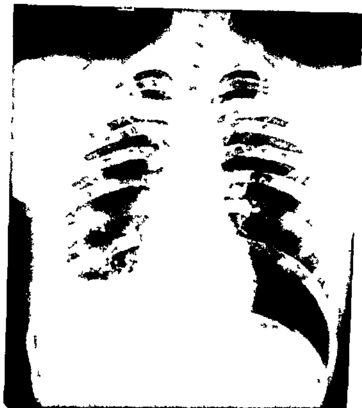


Fig 4 Elevation and flattening of right hemid aphragm following sero fibrinous effusion

and is only slowly converted to a thick purulent exudate Traumatic empyema is discussed in another section of this book

The microscopic characteristics of empyema fluid are similar to those of a pyogenic sero fibrinous exudate with the exception that the former is more purulent It is much easier, however, to differentiate the two on paper than in actual practice All the elements of empyema fluid may be found in pyogenic sero fibrinous effusions The bacterial content number of pus cells and the amount of cellular debris are all propor tionately higher in empyema than in sero fibrinous pleural reactions The difference is one of degree rather than one based on fixed standards Therefore, the line of demarcation between the two is necessarily flexible Until better standards for differentiation are developed we must be content with interpretations based on clinical judgment, past experience and relatively arbitrary standards In view of the foregoing remarks,

any attempt to subdivide empyemas into sero purulent and purulent types must be viewed only with academic interest

Although any pathogenic micro-organism is capable of producing an empyema, the pneumococcus, streptococcus and staphylococcus are the most frequent offenders Pneumococcal emyemas may follow epidemic influenza and measles but more frequently have their origin in lobar pneumonia The empyema is usually metapneumonic and occurs in the convalescent period A thick, creamy, yellow green exudate is characteristic of this complication Streptococcal empyema which complicates streptococcal pneumonias is characterized by a thinner fluid It develops as a simultaneous complication of the underlying pneumonia and is known as synpneumonic empyema The bacteriology of empyemas produced by septic infarction depends upon the nature of the embolus Commonly, pyothorax may be the result of mixed infections This is generally the case in putrid empyemas which frequently complicate bronchiectasis and lung abscess Although anaerobic streptococci predominate in these instances, spirochetes, anaerobic bacilli, fusiform bacilli and other micro organisms are found in myriads Anaerobic bacteria are responsible for the foul and offensive odor of putrid empyemas The presence of gas in the pleural cavity is common in this variety of pyothorax Bronchopleural fistula also gives rise to a rapidly developing mixed empyema The fluid re forms almost as quickly as it can be removed Subdiaphragmatic and hepatic abscess due to the colon bacteria and endamoeba histolytica respectively, infrequently are responsible for empyema Colon bacilli cause a thick, foul smelling exudate while anchovy sauce color may characterize the amoebic infestation

Unlike sero fibrinous exudates which have a tendency to be generalized and fill all recesses of the pleural cavity, empyemas may be more localized and are frequently limited by thick adhesions This characteristic gives rise to the development of loculated empyema cavities which may, or may not, communicate with adjoining pockets (Figs 5A, 5B) When numerous loculations are present, the fluid may be frankly purulent in some and sero fibrinous in others Empyemas are commonly found in the lower thoracic cavity but interlobar (Fig 6), infrapulmonic (Fig 7), apical or mediastinal (Fig 8) locations are not unusual Ordinarily, the mediastinum is flexible and mobile The continued presence of empyema fluid interferes with its flexibility and mobility Later it may become a rigid and fixed structure This is a very valuable asset in the surgical



Fig 5a Multilocular empyema complicating pneumonia of the left lower lobe

management of empyemas In streptococcal empyemas fixation of the mediastinum is delayed and surgical drainage of necessity must be deferred pending the development of this complication The pressure of the empyema fluid causes compression and atelectasis of the underlying lung proportionate to the amount of pleural effusion Naturally small encapsulated empyemas do not cause the same degree of compression The compressed lung is surrounded by the purulent exudate and if the condition remains untreated is soon encased in a thick fibrous capsule This latter development portends serious impairment of pulmonary function On occasion the fibrous tissue covering the lung and pleura may reach great thickness and be as tough as shoe leather

Necrosis and destruction of pulmonary tissue may result from the pressure of empyema fluid. If drainage is not established for the empyema fluid it seeks its own avenue of escape from its pleural confines This may be accomplished by the supervention of a bronchopleural fistula or by



Fig 5b Lateral view same case

empyema necessitatis In the latter instance the fluid burrows through the tissues of the thoracic wall and escapes through a perforation effected by its own pressure and tissue destroying properties This opening is usually in the vicinity of the costo chondral junction of the fifth rib Nature frequently provides a cure in this fashion to compensate for man s ignorance and neglect If the patient survives the empyema, some morbid evidence of its effects may always be detected This mute testimony may be in the form of a thickened pleura thick pleural adhesions a pachypleuritis, a draining sinus, calcification (Figs 9A, 9B) of the pleura or contraction of the hemithorax on the involved side In the latter event, the trachea and mediastinal structures are pulled to the affected side, the interspaces are narrowed, the diaphragm is elevated and the lung is in a varying degree of collapse It may thereafter be the site of chronic infection such as bronchiectasis Associated pericarditis and myocarditis are likewise not at all uncommon in empyemas of long



Fig 6 Interlobar empyema following pneumonia

duration Frequently it is difficult to distinguish between the pericardial and pleural membranes following empyema Occasional empyemas may become sterile and gradually resorb but, as a rule, they rarely terminate spontaneously Generalized amyloidosis is a possible complication

Symptoms and Signs of Pleurisy

Since pleurisy may complicate an endless number of clinical entities, we must be alert to recognize its development without delay A high index of suspicion and familiarity with its clinical manifestations will result in more prompt and correct diagnoses The symptoms and signs of pleurisy fall into two general categories, those associated with fibrinous pleuritis and those found in association with pleural effusions Fibrinous pleurisy is much the more painful of the two At times the pain of fibrinous pleurisy reaches excruciating proportions and may actually be beyond the endurance of even those patients with high pain thresholds Fortunately, this symptom is self-limited Pleuritic pain



Fig 7 Infrapulmonic pleural effusion (left)

originates in the parietal pleura since the visceral pleura and lung are devoid of pain fibers The exact mechanism of pleural pain is still a matter for speculation In some quarters it is felt that pleural pain results only from tension on the parietal pleura As an example they cite the pleural pain associated with pneumothorax Another school of thought attributes pleural pain to the movement of the two inflamed pleural surfaces on each other There is abundant evidence in support of this contention and it is by far the more logical explanation of pleural pain For example the pleuritic pain of lobar pneumonia may be allayed completely by the induction of a small pneumothorax Likewise the development of pleural effusion heralds prompt relief in painful pleurisy

The intensity of a friction rub does not necessarily parallel the severity of the pain In the absence of a demonstrable friction rub however pleural pain is observed only rarely Pleural pain is ordinarily well localized The nerve supply of the lower thorax and diaphragm is such however that pleuritic pain may commonly be referred to distant

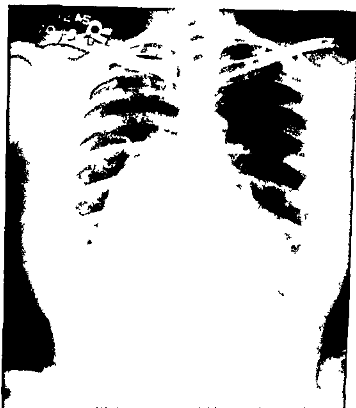


Fig 8 Mediastinal pleural effusion with diaphragmatic tenting and irregular elevation

sites In central diaphragmatic pleurisy the pain is transmitted regularly to the neck and shoulders Since the last six intercostal nerves supply the lateral portions of the diaphragm and the lower thorax painful stimuli from these areas may be referred to the abdomen and back A quick and reliable diagnostic aid is the dramatic relief of pain which can be accomplished with manual pressure on the thoracic wall overlying the *inflamed pleura Unless one is keenly aware of these possibilities* attention may be focused erroneously on the wrong part of the anatomy Ignorance of these facts, unfortunately, has resulted in unwarranted abdominal surgery Although all abdominal viscera may be suspected unjustly in undiagnosed pleurisy, the appendix and gallbladder most frequently are the erroneous objectives of therapeutic surgery

Both dry and wet pleurisy may be associated with varying degrees of dyspnea In fibrinous pleurisy dyspnea is the direct result of voluntary restriction in the range of normal respiratory excursions This compen

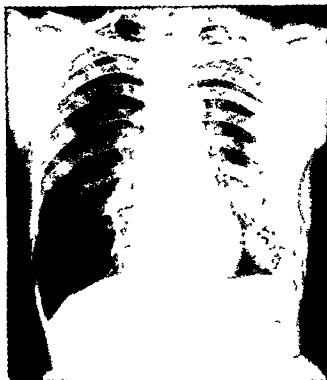


Fig 9a Calcification of pleura, result of empyema following pneumonia in childhood Note flattening and elevation of left hemidiaphragm.

satory measure is designed to allay the severity of the pleural pain which accompanies ordinary respiratory efforts Shallow, rapid abdominal breathing is the result Movement, coughing, sneezing or even talking aggravates the pain. The dyspnea associated with pleural effusions has a mechanical basis It is simply the result of pulmonary compression with a consequent decrease in vital capacity The amount of fluid required to produce the symptoms of dyspnea varies in the individual patient and with the rapidity of the fluid formation Some patients tolerate surprisingly large effusions while others become dyspneic with relatively small amounts Slowly forming effusions allow the gradual evolution of compensatory physiologic reactions so that patients can eventually tolerate large pleural accumulations Additional dyspnea may result from pressure on the contralateral lung and displacement of the mediastinum Cyanosis may be associated with severe dyspnea The



Fig 9b In addition to other differentiating procedures normal lipiodol study of left lower lobe also substantiates the extrapulmonic location of the calcified area

detection of a pulsus paradoxus supplies further evidence of cardio respiratory embarrassment

Useless shallow cough may be part of the picture of both dry and wet pleurisy Severe paroxysmal cough associated with postural changes and productive of large quantities of frankly purulent sputum when detected *clinically is strongly suggestive of bronchial communication* with a pyothorax The febrile reaction varies greatly depending on the etiology and severity of the pleuritis It may be normal or may reach as high as 103-104° F In pyogenic effusions it may be continuous, remittent or intermittent More frequently it is intermittent Chills, high fever and marked toxicity may dominate the clinical picture of pyothorax Close observation of the temperature curve in the con valescent stage of lobar pneumonia will frequently suggest the development of an empyema There is a gradually increasing degree

of daily fever after the temperature has become normal by crisis lysis or therapy Patients suffering from fibrinous pleurisy or sero fibrinous pleurisy may not appear ill Many patients with pleurisy may be very sick Patients with empyema usually are very ill In chronic cases they are weak and debilitated The toxicity of the infection may result in an anemic malnourished patient with a large weight loss and associated multiple vitamin deficiencies Clubbing of the fingers frequently occurs with pyothorax but may disappear following resorption of the exudate Of course the clinical picture of pleurisy differs widely depending on the primary disease process responsible for its development For example the overall signs and symptoms of pleuritis associated with rheumatic fever may differ greatly from those due to tularemia or bronchiectasis

Physical Signs

Although physical examination of the thorax will be generally the same in the various types of pleurisy the findings may be influenced profoundly by the underlying disease process Inflammatory exudates may be bilateral but are generally unilateral

FIBRINOUS PLEURISY (Dry Pleurisy)

On inspection the patient may be dyspneic and is frequently found lying on the affected side Respiratory movement of the involved half of the thorax is usually restricted while the normal side is fuller and more active Breathing may be largely abdominal Cough if present is weak and non productive On palpation the findings of inspection may be verified and additionally a friction rub may be detected The percussion note is usually unchanged on the involved side but a compensatory increase in resonance may be elicited over the contralateral lung If the fibrinous exudate is pronounced the percussion note may be dulled The diaphragm may be found resting at a higher level Auscultation reveals a friction rub Since friction rubs are inconstant and often transient frequent auscultation is indicated If the pleuritis affects the mediastinal pleura and is also in relation to the pericardium the friction rub may be synchronous with the heart beat but is modified by respiration This is known as a pleuro pericardial friction rub The breath sounds on the affected side are usually diminished while on the contralateral uninvolved side they may be intensified

PLEURAL EFFUSIONS SERO FIBRINOUS EMPYEMA

The patient may or may not be dyspneic In the author s experience,



Fig 10 Extreme shifting of all mediastinal contents following pneumococcal empyema in childhood Note deviation of trachea th ckening of pleura and general contracture of right hemithorax with scoliosis

dyspnea has been a more consistent finding of fibrinous pleuritis In the event that dyspnea is present, the patient usually rests on the side of the *effusion and prefers to have the head elevated The interspaces on the* side of the effusion usually bulge, and little, if any, respiratory movement can be detected On the contralateral side the interspaces are widened and the respiratory activity is intensified On palpation the observed *movements of the thorax can be verified Tactile fremitus is decreased* over the fluid but increases in intensity as its superior border is approached Immediately above the fluid level fremitus is increased Rarely a friction rub may be felt In left sided effusions the apex beat *of the heart cannot* be *palpated* The *trachea may* be deviated to the contralateral side The percussion note is dulled over the fluid, but the outlined area of dullness varies with changing positions Greater degrees of shifting may be detected with *less viscid effusions* than *with thicker*

exudates An additional area of dullness may be detected at the base of the normal lung on the back This is known as Grocco's triangle Immediately above the fluid one elicits Skodaic resonance

For academic purposes only, one may outline Ellis' S line If the effusion is on the left, Traube's semilunar space may be obscured On the right, effusions interfere with demarcation of the liver dullness by percussion When effusions involve the left hemithorax, the left border of the heart cannot be percussed and the right border may be found considerably to the right of the sternum. On auscultation the breath sounds and vocal fremitus are diminished or absent over the fluid Rarely a consolidated or atelectatic lung beneath the effusion transmits tubular breath sounds and vocal fremitus Immediately above the fluid level the breath sounds are harsh and tubular, and vocal fremitus is characterized by egophony In left sided effusions the heart may not be heard Occasionally, one may hear a friction rub near the border of the fluid superiorly The breath and voice sounds are increased over the contralateral lung

It is impossible to ascertain the nature of pleural fluid except by thoracentesis The physical findings of pleural effusion as detailed above apply to rather massive accumulations (Fig 11) Naturally, the physical findings will vary as does the amount of pleural fluid The findings of encapsulated and interlobar effusions depend on their location Chronic pleuritis which is a sequel to active pleurisy is characterized by retraction of the thorax on the involved side decreased fremitus, a dulled percussion note and decreased vocal fremitus and breath sounds The physical signs of a thickened pleura are very similar to those of pleural effusion

Diagnosis

The clinical detection of dry or wet pleurisy does not ordinarily offer any serious diagnostic difficulty After a satisfactory history is obtained and a careful complete physical examination is performed, the diagnosis is usually obvious Small pleural effusions, however, are generally evasive on physical examination and as a result they are overlooked frequently by the most astute clinicians Occasionally, small collections of pleural fluid may yield positive physical findings long before Roentgen ray evidence is available Even with the use of special techniques and positions, at least 300 to 400 cc of fluid in the pleural cavity is necessary to produce the changes on which a positive Roentgen



Fig 11 Massive sero-fibrinous effusion Note shifting of heart shadow to contra lateral side

ray diagnosis can be based The diagnosis of pleurisy, nevertheless, is not really as difficult as the determination of its etiology

This discussion is concerned only with non-tuberculous pleural diseases It is estimated conservatively that in excess of 80 per cent of all pleurisies are tuberculous in origin This observation acquires added significance when one considers the fact that the majority of idiopathic *pleurisies also have a tuberculous etiology In view of this fact, the cor* rect etiologic diagnosis of non tuberculous pyogenic and sterile pleurisies should be the rule rather than the exception Success along this line may be achieved regularly by the intelligent utilization of available and indicated diagnostic laboratory aids As previously stated, the primary origin of non-tuberculous pleurisies may be discounted Therefore, accurate specific knowledge of the underlying thoracic, abdominal or other distant and systemic disease processes is essential If this informa



Fig 12 Moderate sized sero fibrinous effusion

tion is available, the etiologic diagnosis of complicating pleurisies presents no special problem

Fibrinous pleurisy may be confused with such clinical entities as incipient herpes zoster of the thoracic wall or intercostal neuralgia The development of typical physical findings, however, soon dispels the confusion Here, again, knowledge of the underlying disease process facilitates early accurate diagnosis Roentgen ray examination of the chest in fibrinous pleurisy is generally of little or no assistance unless blunting of the costophrenic angle is detected

As regards pleurisy with effusion Roentgen ray examination, fluoroscopy and diagnostic thoracentesis afford the most useful and dependable diagnostic aids Typically, in the usual erect postero anterior film of the chest, pleural fluid casts a shadow which is similar in density to that of the heart, diaphragm and subdiaphragmatic organs Generalized inflammatory pleural effusions tend to be unilateral and occupy the

most dependent portions of the pleural cavity They cast a dense shadow which, as a rule, reaches its greatest height in the lateral part of the thorax (Fig 12) Loculated or encapsulated effusions may occupy any part of the pleural cavity or may be confined to the interlobar fissures (Figs 5A, 5B, 6, 7 and 8) Pleural effusions, however, may assume bizarre contours and cast very unusual Roentgen ray shadows To derive the maximum benefits of available roentgenographic aid, the patient should, if indicated, be examined not only in the erect postero-anterior position but films should be obtained in the erect antero-posterior, lateral, oblique, supine, lordotic and lateral decubitus positions The latter position is almost indispensable in the detection of small pleural effusions Examination of the chest in these various positions will reveal the inconsistent and mobile nature of the dense shadow cast by fluid The differentiation of pleural effusion from other endothoracic as well as upper abdominal diseases may be based on these characteristics The Roentgen ray is indispensable in the diagnosis of pleural fluid Relatively large accumulations of pleural fluid frequently yield essentially normal physical findings and may only be suspected and diagnosed by proper Roentgen ray examination

Fluoroscopic examination of the chest is an indispensable adjunct to Roentgen ray studies This procedure provides a means for direct visualization of the altered endothoracic mechanics Limitation of diaphragmatic and other respiratory movements can be observed on the affected side Observation of the compensatory respiratory effort of the contralateral side is also invaluable Additionally, after the introduction of a contrast medium, such as iodized oil, appropriate fluoroscopic and roëntgenographic studies will reveal accurately the boundaries of the pleural fluid When a bronchopleural fistula is suspected, the introduction of iodized oil into the bronchial tree or pleural cavity prior to Roentgen ray examination and fluoroscopy will establish the diagnosis In suspected empyema necessitatis the introduction of iodized oil into a draining sinus may confirm pleural communication Draining sinuses of pleuro pulmonary actinomycosis can be outlined accurately with this relatively harmless technique

The accidental or intentional presence of air in the pleural cavity will provide a straight linear demarcation of the upper limit of the effusion Diagnostic pneumothorax is an effective means of differentiating between pleural, pulmonary and other endothoracic diseases In order to avoid future complications for the patient and interference

with therapy, however, it is advisable to produce only a very minimal degree of pneumothorax Diagnostic pneumoperitoneum is likewise valuable in differentiating between pleural fluid and subdiaphragmatic disease Herniation of the stomach or other portions of the gastro intestinal tract may be very confusing at times The use of diagnostic pneumothorax and pneumoperitoneum may help the solution to this problem A barium meal or enema will yield the final answer Aerograms of the stomach or colon are likewise very valuable diagnostic aids

Unequivocal proof of the existence of a pleural effusion depends on aspiration of fluid by thoracentesis Unless specifically indicated air should not be introduced into the pleural cavity during, or following, diagnostic aspiration Macroscopic examination of the fluid may point to the etiologic diagnosis It is important to note the color, viscosity and odor A thin serosanguineous fluid for example, may suggest a pulmonary infarct while creamy yellow green fluid is typical of pneumococcal pyothorax Foul smelling exudates suggest the presence of anaerobic bacteria Immediate determination of the specific gravity will differentiate quickly between a transudate and an exudate In doubtful instances the protein content of the fluid may be determined The protein level of transudates is generally less than 2 5 per cent Bacteriologic examinations must include a satisfactory stain of a direct smear of the fluid Cultures and other procedures may be indicated Fluid which has developed synpneumonically or metapneumonically should be typed for specific pneumococci If one suspects a malignancy, part of the specimen should be examined histopathologically for the possible presence of neoplastic cells With proper study the determination of the specific etiologic diagnosis in pyogenic effusions is ordinarily accomplished by the well trained physician with relative ease Before withdrawing the aspirating needle, 10 cc of 1 per cent methylene blue or some other suitable dye may be injected if a bronchopleural fistula is suspected In the presence of this complication the sputum will acquire a bluish discoloration in 12 to 24 hours or sooner, depending on the rate of pleural fluid formation and its viscosity When facilities for gas analysis are available, the existence of a bronchopleural fistula may be suggested by a determination of the oxygen and carbon dioxide content of specimens obtained from the pleural cavity This is a tedious procedure and is mentioned in passing only for the sake of completeness

Although proper examination of pyogenic pleural effusions usually

supplies the etiologic diagnosis, in a substantial number of instances the assistance of additional diagnostic, clinical and laboratory aids must be sought For example, a positive blood culture will frequently supply the answer Even the presence of pathogenic parasites in the stool may be significant and related to pleural disease. This is especially true in Loeffler s syndrome and in amoebic disease involving the pleura As a rule, hematologic and urinary studies offer little help in the diagnosis of inflammatory effusions There may be a high leukocytosis with an absolute increase in polymorphonuclear cells This is especially true in pneumococcal pleurisy On the other hand, the white blood count may present no significant abnormality Eosinophiles may predominate in the blood and pleural fluid in the case of Loeffler s syndrome Anemia usually complicates empyemas Proper bacteriologic survey of the sputum with indicated stains and cultures will demonstrate the etiologic agent responsible for the underlying pulmonary disease Gross examination of the sputum may reveal the true primary clinical picture This is the case in bronchiectasis, pulmonary abscess and to a lesser degree in bronchopleural fistula

Skin tests may be used to prove a diagnosis of blastomycosis coccidioidomycosis, actinomycosis, histoplasmosis, and other fungus diseases Casoni s intradermal test is specific for echinococcal disease Precipitin and complement fixation tests are of real value in the diagnosis of virus and fungus disease When significant positive results are obtained they may be considered diagnostic A rising or falling titer is of prognostic as well as diagnostic import in blastomycosis and coccidioidomycosis Specific immunological response to the causative organism producing pleural fluid has also been demonstrated recently

Bronchoscopy may provide excellent assistance in ascertaining the etiologic diagnosis of pleural fluid This is especially true in the case of pulmonary neoplasms Biopsy of local and distant neoplastic lesions should be performed Careful observation of a solitary nodule, a prominent lymph node or an ulcerating lesion will frequently supply the answer to a difficult diagnostic problem If all other diagnostic procedures have failed to establish a satisfactory diagnosis, one may resort to thoracoscopy and, finally, an exploratory thoracotomy

Sterile inflammatory exudates are usually a local manifestation of serious systemic diseases and may be bilateral The diagnosis in these instances is dependent on an accurate assessment of the general clinical findings

In spite of the intelligent use of all available diagnostic aids, in an occasional case of non tuberculous pleurisy the etiology cannot be determined accurately

Treatment

The treatment of pleurisy is both symptomatic and specific Successful management depends greatly on the course of the primary disease which it may complicate Because fibrinous pleuritis is generally very painful early attention should be directed toward the alleviation of this distressing symptom The judicious use of narcotics not only controls the pain but also dispels the patient s apprehension Additionally, strapping of the affected hemithorax with adhesive tape may provide dramatic relief of the pain An occasional patient will be found who has a sensitivity to adhesive tape Therefore it is advisable to question the patient regarding the possible existence of this idiosyncrasy In its presence it is advisable to forego the benefits of this therapeutic measure rather than risk the subsequent complications A wide binder may serve the same purpose Injection of the intercostal nerves over the inflamed pleura with an anesthetic agent such as procaine, cocaine or novacaine also may provide effective relief of the pain Effective relief of pain has been reported following the intravenous use of calcium A hot water bottle is always comforting With adequate control of the pleuritic pain, the patient's clinical condition will show marked general improvement Dyspnea, if due to voluntary restriction of respiratory movement, will soon disappear Before satisfactory relief of the pleural pain is obtained, it may become necessary to administer oxygen to combat dyspnea As the severity of the disease subsides, acetylsalicylic acid will usually provide control of the pain Likewise, it may be used to lower the temperature in the event of a severe febrile reaction The treatment of a fibrinous pleuritis which complicates those clinical entities for which specific therapeutic measures are not available is wholly symptomatic This group, unfortunately, includes a considerable number of very common diseases, and the results obtained with available therapeutic measures are usually discouraging

When pleurisy complicates primary diseases of bacterial origin, the use of specific drugs may be indicated Drug sensitive bacterial pleurisies will respond to specific chemotherapeutic and antibiotic agents Actually, a significant decrease in the incidence of drug sensitive bacterial pleurisies has resulted from the increased utilization of indicated sulfa drug preparations, penicillin, streptomycin, aureomycin, chloromycetin,

terramycin, or other specific agents in the treatment of the responsible primary diseases. The relative infrequence in recent years of empyma following lobar and broncho-pneumonia is an excellent example.

Aside from the added problem of fluid in the pleural cavity, the treatment of sero fibrinous pleurisy is similar to the management of fibrinous pleurisy. As a rule, it is inadvisable to aspirate a sero fibrinous effusion unless the responsible agent is drug sensitive. Careless thoracentesis may convert a relatively harmless sero fibrinous effusion into a troublesome empyema. In the presence of massive effusions resulting in marked dyspnea thoracentesis is indicated. Aspiration of the pleural cavity should be preceded by careful localization of the fluid. This can be accomplished with the aid of physical signs, roentgenograms of the chest in various positions and fluoroscopy. In spite of all possible precautions, unsuccessful and traumatic thoracentesis may be encountered. Even large effusions may be very difficult to locate with the aspirating needle. Prior to aspiration, phenobarbital or some other suitable sedative should be administered. This has the effect of allaying apprehension and also minimizing the possibility of serious accidents due to the use of any of the popular local anesthetic agents. Sodium amytal and aminophyllin should be available for immediate intravenous administration in the event of an untoward reaction. The use of sympathomimetic drugs such as epinephrine hydrochloride in these emergencies is fraught with danger and is contraindicated. Thoracentesis is best accomplished with the patient in a sitting position. A high back rest or the lateral decubitus position may be necessary for those patients who are unable to maintain sitting posture. After proper sterilization of the selected site and satisfactory anesthesia of the skin, subcutaneous tissues and parietal pleura is obtained, an 18 or 19 gauge needle should be introduced carefully into the pleural cavity. Larger gauge needles may be required in thick effusions.

In the author's experience the syndrome of pleural shock was never encountered. If a bloody tap transpires, the aspirating needle should be withdrawn immediately and thoracentesis should be attempted at another site. Generally, it is advisable to introduce the needle near the most dependent part of the fluid. At no time should the operator force air through the needle in an attempt to locate and aspirate the pleural fluid. This practice is very dangerous. Fatal air embolism may result. Successful withdrawal of thick exudates is accomplished more easily and safely after normal saline solution is instilled into the pleural cavity

Management of thick exudates has recently been made simpler and more successful with the intrapleural use of proteolytic enzymes The use of heparin in the pleural cavity to decrease or prevent fibrin formation requires additional investigation before its utilization can be recommended Once a free flow of fluid is obtained the needle may be fixed in place with a small hemostat This precaution will decrease local trauma and avoid accidental laceration of the underlying lung

There is no definite rule regarding the amount of fluid which may be aspirated It is a good practice to remove all the fluid possible before signs of cardio-respiratory distress supervene When the patient complains of a "pulling" sensation in the chest, dyspnea or coughs slightly, thoracentesis must be terminated These symptoms are the result of a too rapid re-expansion of the collapsed lung or a shifting mediastinum with consequent torsion of the great vessels at the base of the heart The introduction of a small amount of air will relieve the symptoms and provide more satisfactory roentgenographic and fluoroscopic localization of the fluid Before the aspirating needle is withdrawn 50 000 units of penicillin should be instilled prophylactically in an effort to prevent secondary infection To avoid draining sinuses the site of entrance should be massaged briskly, and the patient should be encouraged to lie on the opposite side for several hours The latter suggestion may be impossible to observe in the presence of marked dyspnea Subsequent aspirations if necessary, should be performed at other sites in order to avoid local complications When the needle is in place, the patient must never be permitted to move the arm on the ipsilateral side Pulmonary laceration may result or the needle may be broken

If the sero-fibrinous effusion is due to a penicillin sensitive organism, 50,000 units of this drug may be instilled daily, or twice daily, until he fluid is sterile on seven successive cultures or the effusion is resorbed Once a sero-fibrinous exudate resorbs it does not tend to recur The introduction of concentrated penicillin solutions into the pleural cavity may be accompanied by pain or severe febrile reactions If sufficient fluid remains in the pleural cavity, it will act as a diluent for the penicillin Otherwise, it is best to dissolve the penicillin in normal saline in such proportions that the resulting solution will not contain more than 500 to 1,000 units per cc If the organism is penicillin resistant, streptomycin may be substituted As much as 500 000 units may be instilled once or twice daily The concentration of streptomycin should not exceed 10,000 units per cc Simultaneous administration of systemic chemo-

therapeutic and antibiotic agents is necessary to obtain a lasting cure. Both penicillin and streptomycin are absorbed from the pleural cavity General drug allergy has been observed after the intrapleural use of these drugs without concomitant or previous systemic administration To accelerate recovery from this complication, the pleural cavity should be evacuated and thoroughly washed with a solution of normal saline

Prior to the era of antibiotics, it was the general tendency, for various reasons, to avoid aspiration of both bacterial and non bacterial sero-fibrinous pleural exudates unless absolutely necessary Some men still adhere to this restriction The intelligent use of indicated antibiotics in bacterial sero fibrinous pleural effusions, unquestionably, prevents the development of a large number of empyemas The very satisfying experience with repeated antibiotic instillation and aspiration in indicated cases of bacterial sero fibrinous exudates supports the continued use of this therapeutic and prophylactic practice All bacterial sero-fibrinous effusions should be considered potential empyemas and treated accordingly

The successful treatment of pyothorax depends on the accomplishment of the following objectives sterilization and removal of the fluid and obliteration of the empyema cavity with subsequent re expansion of the lung The overwhelming majority of non tuberculous empyemas is due to the pneumococcus, streptococcus and other bacteria with known susceptibility to available antibiotic agents Non surgical achievement of the enumerated objectives in the treatment of these empyemas depends on the intelligent utilization of indicated antibiotics systemically and locally The method of treatment is generally the same as that recommended for antibiotic susceptible sero-fibrinous exudates There are a few important differences in technique The fluid must be aspirated completely each day and the pleural cavity washed with normal saline solution Additionally, the intrapleural use of proteolytic enzymes should be routine Re expansion of the lung should not be too rapid Loculated collections of pus may develop if re-expansion occurs before sterilization of the pleural cavity is accomplished Once sterility of the pleural cavity is achieved, re expansion of the lung should proceed without restriction It is imperative to follow the condition of the lung with daily

... the duration

mation regarding the endothorax and facilitate intelligent ...

management of each case Conservative management must be abandoned, however, if demonstrable evidence of clinical and bacteriological improvement is not apparent after three or four days of treatment Failures are common in mixed, putrid, encapsulated and multiloculated empyemas Likewise, empyemas which develop in spite of antibiotic therapy for the primary disease are also apt to resist conservative management Empyemas associated with bronchopleural fistulae rarely respond to this form of therapy Poor results predominate the overall clinical results achieved in the treatment of chronic empyemas In cases of empyema necessitatis due to antibiotic-sensitive bacteria, medical management is usually successful The sinus will be obliterated and healed after the pleural cavity s freed of infection Empyemas due to septic pulmonary infarction may also respond to conservative management only to recur each time an infected embolus lodges in the lungs Lasting cures in this instance will be achieved only after proper surgical treatment of the primary disease In the face of therapeutic failure, conservative management of empyema should be abandoned The patient should be given the benefit of surgical treatment without undue delay Systemic and local administration of antibiotic agents in indicated cases prior to surgical intervention will augment the therapeutic benefits of surgery Postoperatively, the use of systemic and local antibiotic therapy is definitely indicated and unquestionably exerts a beneficial effect on the course of the disease

Supportive therapy in the conservative and surgical management of empyema is very important One should pay attention to the general condition of the patient Maintenance of a satisfactory state of nutrition is an essential prerequisite to successful conservative or surgical treatment of empyema patients Anemia, malnutrition and avitaminosis are quite common Anemia should be treated with repeated blood transfusions The treatment of malnutrition and avitaminosis requires a nutritious diet high in carbohydrate, protein and vitamin content The diet should be supplemented with additional vitamins by mouth or parenterally Occasionally, the use of any of the popular protein preparations is indicated Other complications are treated as they arise

Successful treatment of pyothorax requires the close co-operation of the internist and thoracic surgeon Both must be open to suggestion and constructive criticism If a feeling of mutual respect for each other's opinions prevails, patients with empyema will derive the full therapeutic benefits of co-operative medical and surgical management of their disease.

MECHANICO CIRCULATORY DISEASES OF THE PLEURA

General Remarks

Physical changes in the thorax, altered capillary fragility and permeability and physico chemical changes in the blood, individually or in varying combinations, are responsible for this large heterogeneous group of important pleural diseases In these conditions, changes in the pleura proper are usually minimal, or absent, as contrasted with the definite alterations of the membrane characteristic of inflammatory diseases Nevertheless, mechanico-circulatory diseases of the pleura are only the secondary manifestations of usually serious primary disease processes The pathogenesis and pathology of some of these pleural entities, such as effusion associated with Meigs syndrome or with cirrhosis of the liver, are not too clearly understood Systemic, thoracic, abdominal and other distant disease foci may be responsible for mechanico circulatory disturbances of the pleura The latter are all characterized by the abnormal presence of fluid or gas in the pleural cavity The type of abnormal pleural content affords a convenient and satisfactory basis for subdividing mechanico circulatory diseases of the pleura into four general groups hydrothorax hemorrhagic pleural effusion, chylothorax and pneumothorax

HYDROTHORAX

The presence of a non inflammatory serous effusion in the pleural cavity is known as hydrothorax This type of fluid is a clear, pale, straw colored transudate free of debris and does not clot on standing Its specific gravity is always less than 1 018 and, as a rule, varies from 1 012 to 1 014 The protein content may reach 2 5 per cent but is invariably less than 4 per cent Desquamated endothelial lining cells and a few lymphocytes constitute the cellular content These characteristics of a transudate differentiate it from an exudate If lymphocytes are present in unusually large numbers, a transudate may be confused with a tuberculous effusion until additional differentiating studies are completed

Hydrothorax may be bilateral, but, in association with such clinical entities as Meigs syndrome, cirrhosis of the liver or congestive heart failure, it shows an unusual predilection for the right hemithorax Hydrothorax most frequently is the result of cardiac or renal failure As previously stated, it usually occupies the right hemithorax in cardiac failure but may be bilateral and, on rare occasions, only the left pleural

cavity is involved Loculated pleural effusions have also been observed in occasional cases of cardiac decompensation In renal failure such as that which accompanies true nephrosis or the nephrotic stage of nephritis it is usually bilateral Effusions of the right hemithorax characterize both cirrhosis of the liver and Meigs' syndrome The exact mechanism responsible for the pleural transudate in both of these instances and their almost uniform presence in the right hemithorax is a fact without reasonable explanation As originally described, Meigs' syndrome was characterized by fibroma of the ovary, ascites and the presence of an effusion in the right hemithorax Recently, however, thecomas, multilocular cystadenomas and other benign pelvic tumors have also been identified with Meigs syndrome Anemia, malnutrition, wet beri beri, the pressure of intrathoracic tumor masses, thrombotic occlusion of large endothoracic veins and the mechanical effect of a good sized pneumothorax may also be responsible for hydrothorax

The signs, symptoms and diagnosis of hydrothorax are generally the same as those of inflammatory effusions Therapeutic management of hydorthorax depends entirely on the nature and progress of the underlying disease process To relieve annoying dyspnea, thoracentesis may be performed when indicated The beneficial effects of this symptomatic measure, however, are relatively short lived Unless the responsible primary cause is eliminated, the fluid re accumulates rapidly Since transudates are excellent culture media for bacteria, thoracentesis should be avoided or delayed if possible Flawless sterile technique must be observed or else the risk of superimposed bacterial infection will dwarf the expected therapeutic benefits Surgical removal of the pelvic tumor in Meigs' syndrome results in complete and permanent resorption of the hydrothorax

Hemorrhagic Pleural Effusion

The presence of frank blood in the pleural cavity is known as hemothorax It is usually due to thoracic trauma or rupture of a thoracic aneurysm When the pleural fluid contains enough red blood cells to produce pink or reddish color but is not frank blood, it is referred to as a hemorrhagic effusion A minimum of 5 000 to 6,000 red blood cells per cubic millimeter is required for the production and gross recognition of hemorrhagic effusions The color of the fluid depends on the condition as well as the number of the red blood cells Degeneration of the red corpuscles is followed by changes in the hemoglobin which may produce a brown or amber colored effusion In hemorrhagic pleural

effusions, eosinophilic cells may be present in unexplained large numbers and examination of the circulating blood *may also reveal an absolute* eosinophilia

Under certain conditions any pleural effusion may become hemorrhagic Primary and metastatic malignancies of the pleura, however, are responsible for about 85 per cent of all hemorrhagic effusions This complication *is likewise not an uncommon finding in association with* such clinical entities as pulmonary infarction, congestive heart failure leukemia, thrombocytopenic purpura hemorrhagica, cirrhosis of the *liver, pneumonia* rheumatic fever or nephritis Although tuberculosis of *the pleura is not* within the province of this discussion, the author wishes to state for the sake of *completeness that he has observed hemorrhagic* effusions in association with this disease only rarely This observation differs sharply from previous teachings and prevailing popular clinical opinions on the matter The presence of traumatic blood in aspirated fluid *at the very beginning or at the conclusion of thoracentesis must* not be confused with hemorrhagic pleural effusions

The signs symptoms and methods of diagnosis of hemorrhagic *pleural effusions are generally similar to the observations made in connection with the discussion of the other types of pleural effusions* Treatment depends on the type of the original fluid and the nature of the primary disease

CHYLOTHORAX

Medical dictionaries define chylothorax as the presence of milky fluid in the pleural cavity True chyle, chyliform fluid and pseudo *chylous effusions are all included in this loose non specific definition* Consequently much unnecessary confusion has resulted from the defined *use of the word In this presentation* the use of the term chylothorax is restricted to the designation of chyle in the pleural cavity Pseudo chylous or chyliform fluids are regarded as peculiar or complicating characteristics of certain non *chylous pleural effusions Some clinicians and pathologists have even* attempted to differentiate between pseudo *chylous and chyliform effusions This practice has resulted,* unfortunately, in only additional confusion If both terms are retained, it is best that they be used interchangeably *Chyle contains varying amounts* of emulsified fats Macroscopically, it has an opalescent homogeneous milky appearance After standing, a creamy supernatant layer may develop Clotting may also occur, but this is an uncommon *character*istic The fat content *may vary from 0 4 per cent to 4 0 per* cent, and

its presence may be verified by staining the fluid with Sudan III Microscopic examination of an unstained specimen reveals its oily nature Removal of the fat and clearing of the fluid may be accomplished by shaking an alkalinized specimen with ether The reaction of chyle is alkaline, and its specific gravity is greater than 1 012 Proteins and white blood cells are present in variable amounts Lymphocytes, however, are the predominating cells Unless secondarily infected, the fluid is sterile and usually odorless These are the characteristics of chyle which readily differentiate it from the pseudochylous fluid of long standing encysted effusions, lipoid nephrosis or effusions associated with the nephrotic stage of glomerulonephritis Microscopically, pseudochylous effusions have a more homogeneous appearance than chylous fluid

Chylothorax has been recognized with increasing frequency in recent years and is by no means as rare as previously believed It may occur at any age but is relatively uncommon in infancy Malignant involvement of the thoracic duct, its tributaries, the left subclavian vein or other large veins of the thorax is most frequently responsible for the development of chylothorax Malignant invasion of one or more of the enumerated vessels or direct pressure of the tumor mass on any of these structures may result in this complication Tumors of the lymphoblastoma group are commonly responsible for chylothorax The presence of chyle in the pleural cavity is due to trauma in about one-third of the cases Perforating lymphangitis, the pressure of inflammatory endothoracic lymph nodes, cirrhosis of the liver, filariasis or ruptured aneurysms of the thoracic duct may also cause chylothorax Spontaneous rupture of the thoracic duct occurs most frequently in infants Since the thoracic duct traverses the greater [illegible] t of the verteb[illegible] that side [illegible] left side [illegible] pleural structure Consequently, chylous fluid may be present in the extrapleural space for considerable periods of time before entering the pleural cavity

In addition to the usual signs and symptoms of fluid in the pleural cavity, chylothorax is associated with other characteristic clinical findings Emaciation, malnutrition, oliguria and thirst may all be manifest The severity of the symptoms varies with the degree and duration of the chylothorax. The author once observed the development of a peptic ulcer followed by fatal hemorrhage in a young child of seven suffering

from chylothorax In this case the marked hypoproteinemia was thought to be responsible for the development of the ulcer *The diagnosis of* chylothorax is easily established after aspiration and examination of the pleural fluid

The treatment of chylothorax is generally unsatisfactory When trauma is the responsible cause, healing of the thoracic duct and subsequent recovery may be expected *in about 50 per cent of the cases* The results are uniformly poor when chylothorax is due to malignancy Irradiation of radio-sensitive lymphoblastomas may give temporary relief General symptomatic measures directed at maintaining a satisfactory state of nutrition are essential The replacement of lost proteins and fats should receive special attention Any attempt to accomplish this objective, especially in cases due to malignancy, usually ends in failure Intravenous readministration of chyle aspirated from the pleural cavity has been tried The results of this form of therapy are likewise not only equivocal but frequently fatal Surgical repair of the thoracic duct in spontaneous chylothoraces and those due to trauma is a very difficult undertaking and usually ends in failure The results achieved from paralysis of the corresponding hemidiaphragm or the induction of an artificial pneumothorax are also very discouraging Since chyle re accumulates *very rapidly after thoracentesis*, this measure should be avoided if possible and reserved for the alleviation of severe dyspnea Aspiration offers only temporary symptomatic *relief* and *may initiate* a harmful vicious cycle

PNEUMOTHORAX

Etiology The presence of air or other gas in the pleural cavity is known as pneumothorax Normally, the pleural cavity is a vacuum with flexible boundaries Pneumothorax may be spontaneous, traumatic or induced Spontaneous pneumothorax may complicate any disease of the pulmonary tissue or other thoracic structures Pneumothorax usually involves the entire pleural cavity but may be a localized pocket *Although pulmonary or pleural tuberculosis is admittedly a very com*mon cause of spontaneous pneumothorax, many other pulmonary diseases such as emphysema, *asthma bronchiectasis, lung abscess some* of the pneumoconioses septic infarction pneumonia cancer, subpleural blebs or cystic disease of the lungs are capable of producing this complication Under certain conditions air may also enter the pleural cavity from the esophagus, stomach or some portions of the intestinal tract which are in close relationship to the infradiaphragmatic surface Mediastinal

emphysema frequently has an associated pneumothorax Empyema may produce pneumothorax either by destruction of the underlying pulmonary tissue and subsequent bronchial communication or it may result from the metabolic activity of gas producing bacteria present in the purulent fluid Fortunately, production of a pyopneumothorax due to empyema is rather infrequent As it often happens however the reason for the development of a spontaneous pneumothorax cannot be assigned to a definite cause Consequently, there is a relatively large group of spontaneous pneumothoraces which are classified as simple or idiopathic Purposefully induced pneumothoraces are usually established for diagnostic or therapeutic purposes This presentation is not concerned with therapeutic tuberculous or traumatic pneumothorax The remarks in this discussion are therefore, limited to spontaneous pneumothoraces resulting from non tuberculous diseases Diagnostic pneumothorax was mentioned in a previous section and likewise requires no additional comments



Fig 13 Simple Pneumothorax (idiopath c')

Pathology and Pathogenesis Of all the various clinical entities which may be responsible for spontaneous pneumothorax, the simple or id o pathic variety has attracted the greatest attention and speculation (Fig 13) Many explanations have been proposed but none is universally acceptable Rupture of a sub pleural bleb however, is the most acceptable popular explanation today Only on rare occasion can the subpleural bleb be demonstrated while the patient is alive Postmortem examination of the pleura of patients who experienced idiopathic spontaneous pneumothoraces in life is almost as discouraging No evidence of pleural tear can be demonstrated in the overwhelming majority of cases and the pleura usually appears perfectly normal macroscopically and microscopically In the past it has been customary to assign all unexplained spontaneous pneumothoraces to a tuberculous etiology, but in recent years evidence has accumulated to decelerate this tendency Many cases of spontaneous pneumothorax have been carefully studied and followed The incidence of subsequent tuberculous infection in these instances has been very small Reliable investigators have concluded that it is only slightly greater than the expected incidence of tuberculosis in the general population Simple spontaneous pneumothorax is most frequent during the more active years of life It occurs in otherwise normal individuals Men are more frequently affected than women Spontaneous pneumothorax is usually unilateral but may be bilateral especially if the two pleural cavities communicate as they do in rare instances Not uncommonly a patient may experience recurrent episodes of simple spontaneous pneumothorax The author recalls one of his medical students who experienced at least eight known attacks in four years Although a familial tendency has not been established numerous instances of simple spontaneous pneumothorax occurring in several members of the same family have been observed Simple spontaneous pneumothorax may occur during periods of absolute rest but is more frequently associated with some form of physical exertion such as sneezing coughing laughing yawning or straining at stool The signs symptoms and treatment of the condition depend entirely on the extent of the pneumothorax and degree of positive pressure changes in the pleural cavity

Pathological Physiology Depending on the nature of the pleural defect three types of spontaneous pneumothorax are recognized the closed the open and the valvular or tension pneumothorax Gas analysis of the contents of the pleural cavity will differentiate the closed type of pneumothorax from the other two varieties In the closed type the oxygen con

tent of the pleural gas ranges up to 5 per cent A higher content indicates communication with the outside air This method of determining the type of pneumothorax is too involved Rapid determination of the type of pneumothorax may be established by obtaining manometric readings of the intrapleaural pressure This method is reliable and preferable to that of gas analysis The trend of events in the pleural cavity is reflected accurately in a serial study of manometric pressure determinations In the closed variety the pressure in the pleural cavity experiences only a moderate alteration The manometric readings do not exceed 0 cm of water The extent of the pneumothorax is very moderate, and symptoms are either absent or so minimal that the condition is unquestionably frequently overlooked As previously mentioned the pressure in the normal pleural cavity with usual respiratory effort is always negative or sub atmospheric This negative pressure represents the differential between the elastic recoil of the pulmonary tissue and the less yielding thoracic wall In the open type of pneumothorax atmospheric pressure prevails in the pleural cavity because the communication with the bronchial tree is constant Symptoms in this instance are usually more severe than in the closed type The open type of pneumothorax may persist for long periods of time before the opening in the pleura closes and the air is resorbed Finally, in the tension type of pneumothorax the valve like arrangement of the defect in the pleura permits air to enter the pleural cavity but none can escape At first air enters the pleural cavity with each inspiratory effort As the intrapleural pressure becomes more positive and the amount of air in the pleural cavity increases, however, the hemithorax is immobilized Consequently, the lung on the same side becomes atelectatic and useless When this circumstance develops, air no longer enters the pleural cavity during inspiration but only passively during the expiratory effort of the contralateral side If the mediastinum is mobile, spontaneous pneumothorax of one hemithorax always exerts a deleterious compressing effect on the contralateral lung Pulmonary function and vital capacity are further impaired in this manner The resulting clinical signs and symptoms may assume alarming proportions Mediastinal herniation due to pneumothorax is not uncommon (Fig 14) This complication can be best demonstrated by fluoroscopic examination of the chest in various phases of respiration It is indeed fortunate that most spontaneous pneumothoraces, even if open or valve-like to begin with, are soon converted to the closed variety In the absence of this fortuitous chain of events, spontaneous pneumothorax



Fig 14 Mediastinal hernia.

would present a more formidable therapeutic problem and terminate fatally with greater frequency

Spontaneous pneumothorax may complicate or be complicated by the presence of fluid in the pleural cavity The pneumothorax is then identified by the proper descriptive prefix as *hydropneumothorax* (Fig 15), hemopneumothorax, chylopneumothorax, serofibrinous pneumothorax and pyopneumothorax (Fig 16) There is a widespread tendency to use the term *hydropneumothorax* to specify a *pneumothorax* with a sero fibrinous effusion This erroneous confusing practice should be avoided Clinically detectable fluid in the pleural cavity is generally present in all spontaneous pneumothoraces The quantity varies greatly from insignificant amounts to effusions of significant proportions Hydropneumothorax may develop very rapidly and give rise to severe symptoms The author once observed the development of a severe hydropneumothorax in a matter of hours It filled the entire pleural cavity and caused



Fig 15 Hydropneumothorax complicating congestive heart failure

sufficient pressure to produce an obstruction to the venous return from the head, neck and upper extremities

Signs and Symptoms The signs and symptoms of spontaneous pneumothorax vary with the type and degree of pneumothorax produced The clinical picture is likewise influenced by the condition of the underlying lung, the mobility of the mediastinum and the amount of cardiac and pulmonary reserve Additionally, the condition of the pleura has a profound influence on the nature and course of the clinical manifestations As previously stated, spontaneous pneumothorax may be associated with very few, or no, observable signs or symptoms These cases are usually discovered accidentally during routine roentgenographic or fluoroscopic examination of the chest The majority of recognized cases, however, manifest significant although varying signs and symptoms

The average case of spontaneous pneumothorax is ushered in by a severe pain in the corresponding hemithorax It may develop during a

hernia, a barium swallow will establish the abnormal presence of the stomach in the thorax As a rule, the diagnosis of pneumothorax is quite simple

Treatment The treatment of spontaneous pneumothorax depends entirely upon its type and extent Closed pneumothoraces usually require only symptomatic care The amount of time required for the resorption of the gas depends upon the size of the pneumothorax and the condition of the pleura Usually, even the larger ones disappear within one month, and with the smaller ones it is only a matter of days Indicated analgesics and sedatives of choice may be used, respectively, for the control of pain and apprehension Occasionally, the use of oxygen is warranted Aspiration of the pleural gas is rarely necessary Follow up examinations at regular frequent intervals are indicated to rule out serious responsible primary disease If simple spontaneous pneumothorax recurs frequently, it may be advisable to establish pleural symphysis To accomplish this objective the introduction of various irritants into the pleural cavity has been recommended In this connection the use of the patient's own blood, 50 per cent dextrose solution, the insufflation of various powdered substances such as ordinary talc and a therapeutic trial with other materials have been advocated In the author's hands the results obtained with these measures have been equivocal Since the resulting aseptic pleuritis may be quite troublesome, this form of therapy should be reserved for the more serious types of pneumothoraces The best treatment for the mild closed type is bed rest and symptomatic therapy

Treatment of the open type of pneumothorax is generally similar to that of the closed variety Paralysis of the hemidiaphragm on the affected side may be beneficial Tension pneumothoraces require immediate heroic therapy The use of a water trap is indicated in all these cases To obtain the maximum benefit without delay, a 16 gauge needle should be inserted in the thorax It should be introduced only far enough to permit the escape of the gas trapped in the pleural cavity If it projects too far into the endothorax, additional tears in the pleura may result from coughing or any other activity which brings the visceral pleura closer to the thoracic wall The glass outlet tube should project no more than one centimeter below the level of the water in order to obtain satisfactory results When bubbling ceases, the rubber tubing may be occluded temporarily with a suitable clamp After a satisfactory period of observation, if the patient manifests no further signs or symptoms of increasing pressure in the pleural cavity, the water trap may be

disconnected Before removing the needle from the chest, it is advisable to obtain a manometric reading of the intrapleural pressure Since tension pneumothorax represents a real medical emergency, no time should be lost in reducing the intrapleural pressure Sterile technique is desirable in accomplishing this result, but on occasion there is no time for sterilizing the skin or for the production of a satisfactory local anesthesia The introduction of the needle into the chest without any delay is the paramount objective in the event of tension pneumothorax When pneumothorax and pleural effusions are coexistent, therapeutic considerations are influenced chiefly by the nature of the fluid involved The management of the various types of pleural effusions is discussed in previous portions of this presentation

NEOPLASTIC DISEASES OF THE PLEURA

Tumors of the pleura may be primary or secondary Primary tumors are exceedingly rare while secondary tumors are not uncommon The most important and only primary malignancy of the pleura is the mesothelioma In the 19th century the term, "tubercle like lymphadenoma," was used to describe this tumor Later the name, "endothelioma," was proposed for this malignancy because it was ascribed to a vascular origin Recent reliable investigations together with the fact that the pleura is a mesodermal derivative have established the term mesothelioma as a more descriptive and appropriate identification of this tumor

Tumors arising in the pleura will display both epithelial and mesenchymal characteristics Mesotheliomas are ordinarily composed of large epithelioid cells separated by collagenous fibers of tumor cell origin The cellular elements have a tendency to arrange themselves as alveolar rests or rows Unfortunately, not all pleural mesotheliomas present this typical histopathologic pattern Pleomorphism and multidirectional lines of evolution complicate the proper identification and classification of this new growth This tendency to frequent deviation has been paralleled by equally numerous attempts by well intentioned investigators to prove the existence of more than one type of primary pleural malignancy The problem of pleural malignancies, consequently, is clouded and confusing Conclusive investigation and authoritative evaluation of this controversial problem have been limited by the paucity of cases available for study Only one, and probably less than one, case in every one thousand postmortem examinations is a proved pleural mesothelioma If primary malignancies of the pleura do occur, the weight of the available evidence

supports the contention that they are all mesotheliomas with inherent possibilities of wide structural variation

This opinion, however, is not shared by all clinicians and pathologists There is a sizable group of reliable investigators who do not admit the possible existence of primary tumors of the pleura This contention is a very disarming possibility when one considers the large volume of literature which has been written on the subject of pleural mesotheliomas by innumerable reliable investigators It is true, nevertheless, that many pleural tumors diagnosed originally as mesotheliomas are proved eventually to be metastatic lesions from the underlying bronchopulmonary tissue or neighboring thoracic and even more distant organs A small primary malignant nodule in the lung is not infrequently the source of widespread pleural involvement Unless the pulmonary tissue is examined diligently in all cases of suspected pleural mesothelioma, a small primary tumor nodule may be overlooked A high index of suspicion should be maintained at all times regarding this possibility in order to avoid erroneous diagnoses of pleural mesothelioma Primary malignancies frequently arise in relation to the parietal pleura They have their origin in the fascia of the intercostal muscles, nerve sheaths and other thoracic structures Angiosarcomas, lipomyxosarcomas, neurosarcomas, round cell or spindle cell sarcomas, rhabdomyosarcomas or chondrosarcomas which arise from these tissues may be attributed erroneously to a pleural origin because of the intimate relationship of the parietal pleura to the structures of the thoracic wall The known pleomorphic potentialities of pleural mesotheliomas contribute to this pitfall in diagnosis After careful consideration, this author is satisfied to conclude that such an entity as pleural mesothelioma does exist That it probably occurs much less frequently than one time in every 1,000 postmortem examinations also appears to be a valid assumption

There are no primary benign tumors of the pleura Just as the tumors which arise in relationship to the parietal pleura are malignant, those which occur in association with the visceral pleura are ordinarily benign Fibromas, lipomas and chondromas have their origin in the subserous connective tissues Giant sarcomas which arise in relation to the visceral pleura do not possess metastatic or invasive properties They grow slowly but may attain tremendous size Primary tumors which arise in relation to the visceral pleura, with the possible exception of giant sarcomas, are asymptomatic They are very small and usually discovered

only by accident during surgical procedures or postmortem examinations Surgical excision of these growths is the method of treatment

Metastatic malignancies of the pleura are common Any tumor which is capable of producing metastases may involve the pleura Metastatic pleural lesions are most frequently secondary to tumors of the underlying bronchopulmonary tissue. Tumors of the breast also involve the pleura with great frequency Malignant lesions of the esophagus are a frequent source of metastatic pleural involvement Tumors of the other thoracic structures, stomach, adrenals, prostate, thyroid, pancreas and uterus are additional common sources of pleural metastases Whenever a pleural malignancy is discovered it is imperative that these and other sites in the body be carefully scrutinized for a possible source of metastasis

Primary or metastatic lesions of the pleura may be diffuse or localized Either variety produces hemorrhagic pleural effusions Any unexplained pleural effusion, whether hemorrhagic or otherwise, however, in individuals past the age of 40, should arouse strong suspicions of a possible underlying malignant process The chemical, physical and cytologic characteristics of the fluid depend upon the nature of the malignancy, duration, location and extent of pleural involvement Occasionally the effusion develops the characteristics of a true hemothorax

The tendency to rapid reaccumulation following thoracentesis is a regular characteristic of effusions produced by malignant diseases of the pleura Following the detection of hemorrhagic pleural effusion, indicated clinical and laboratory study to establish the correct etiology is in order However, one should bear in mind that a hemorrhagic pleural effusion is a possible manifestation of such clinical entities as pulmonary infarction, congestive heart failure, thrombocytopenic purpura hemorrhagica, cirrhosis of the liver, pneumonia, rheumatic fever, nephritis or pulmonary tuberculosis Under certain conditions any pleural effusion may become hemorrhagic Primary or metastatic malignancies of the pleura, however, are responsible for about 85 per cent of all hemorrhagic effusions Although roentgenographic and fluoroscopic examination of the chest are without rival in detecting pleural reactions, accurate identification of the etiologic factor depends upon other clinical and laboratory studies

Diagnostic thoracentesis should be performed as soon as the presence of a pleural effusion has been determined An anti coagulant should be added to the aspirated material to avoid clotting Complete withdrawal of the effusion should be attempted in order to facilitate more satisfactory

roentgenographic examination of the underlying lung Should the symptoms of dyspnea, cough, pulling sensation or pain in the chest develop during the procedure, the introduction of a small quantity of air usually suffices to control these manifestations of changing intra thoracic pressures and position of the heart and great vessels Aspiration of the effusion may then be continued until all the fluid is withdrawn repeating small injections of air as necessary Production of pneumothorax in the presence of a hemorrhagic pleural effusion due to a malignancy is actually desirable for diagnostic purposes Introduction of air should be minimal or avoided after the diagnosis is established Since bloody effusions are excellent culture media for bacteria strict asepsis must be practiced in performing each thoracentesis To avoid trouble some complications such as pyohemothorax penicillin or any other suitable antibiotic agent should be instilled into the pleural cavity and along the needle tract when the thoracentesis is completed

Determination of the specific gravity and chemical analysis of hemorrhagic pleural effusions due to a malignancy are of no diagnostic value The fluid may be thin and easy to aspirate or very thick and gelatinous and difficult to remove Cytologic examination of properly prepared specimens of the hemorrhagic fluid by a competent histopathologist is the most important diagnostic study Frequently malignant cells will be detected in the aspirated material Tumor identification usually follows Unfortunately, even in the presence of a known malignancy malignant cells cannot always be detected in the pleural fluid in spite of repeated diligent study

If identification of the tumor does not follow pleural fluid examination other diagnostic studies should be considered A careful search for enlarged lymph nodes or overt tumor growths in the immediate thoracic or more distant regions of the body may be fruitful The breast thyroid uterus and prostate deserve special attention Surgical biopsy of an abnormal lymph node or other lesion may provide the diagnosis after histopathologic study Aspiration biopsies of the pleura are generally failures Punch biopsies with a Vim Silverman needle are more successful in these instances Larger and more satisfactory pieces of tissues are made available for study by this latter procedure Many condemn the use of aspiration or punch biopsies because of the possible danger of stimulating or actually producing metastatic lesions In the presence of malignant pleural effusions one need not hesitate to perform either an aspiration or punch biopsy of the pleura This observer has heard and

read many reports of secondary seeding and metastasis following either of these procedures but has never experienced or witnessed these misfortunes Furthermore, how much significant harm can one produce in the presence of either a primary or secondary pleural malignancy? Actually, and with rare exceptions, determination of an accurate diagnosis in these instances is of academic interest only

Since malignant tumors of the pleura are frequently secondary to primary lesions of the bronchopulmonary tissue bronchoscopic examination should be performed routinely The responsible primary tumor may be visualized Specimens of bronchopulmonary secretions and frequently biopsy material may be obtained in this fashion for histopathologic review Additionally, careful study of the position and configuration of the bronchoscopically accessible portions of the tracheobronchial tree may be of valuable diagnostic assistance Bronchography should be used for indirect visualization of those portions of the tracheobronchial network which are inaccessible for direct bronchoscopic study Careful roentgenographic and fluoroscopic examinations of the lung in various positions are especially helpful Examination of the gastrointestinal tract with an opaque material may reveal the source of pleural metastasis A high serum acid phosphatase level will incriminate the prostate Alkaline phosphatase determination is of no special value If existence and identification of a malignancy is not established or confirmed by the enumerated procedures, one should not hesitate to recommend thoracoscopic examination of the pleura and, preferably, a diagnostic thoracotomy Many other diagnostic procedures may be attempted In this presentation, however, only those procedures which are most frequently indicated, practicable and generally useful have been discussed and evaluated

Since mesothelioma is considered the only primary malignancy of the pleura, it deserves some special attention Pleural mesotheliomas may occur in all ages, but are most frequent in the adult age group Males are affected twice as often as females Both hemithoraces are probably involved with equal frequency but opinion is divided on this point The onset of the tumor is insidious Non-productive cough and pain in the chest are early symptoms Fever becomes a manifestation when secondary infection supervenes but may occur without this complication Later, the cough may acquire expectorant qualities Massive accumulation of a hemorrhagic pleural effusion occurs with distressing regularity Dyspnea ensues and quickly assumes the position of paramount concern

among all other symptoms The patient becomes cachetic with startling rapidity Loss of weight, anemia and weakness are typical observations Dependent edema may occur at any stage of the illness The panorama of symptoms changes frequently to correspond with the rapid growth of the tumor Frequent thoracenteses are indicated for the palliative relief of dyspnea Resistance to the introduction of the aspirating needle may be marked As previously indicated, the benefits of thoracenteses are very temporary since the fluid re accumulates rapidly Occasionally daily thoracenteses are necessary to relieve the cardio-respiratory embarrassment The fluid is easily aspirated early in the illness but gradually it becomes thicker and more difficult to remove Re accumulation has been observed to occur less rapidly after the pleural fluid assumes a thicker character There is no effective treatment for pleural mesothelioma, or any other malignant involvement of the pleura Metastases are common and the tumor may extend to involve the other pleural cavity pericardium peritoneum and capsules of abdominal viscera Patients usually die within six to 12 months following detection of the tumor

EPIDEMIC PLEURODYNIA

By Andrew L Banyai, M D and J Winthrop Peabody, M D

Epidemic pleurodynia was recorded as early as 1856 by Finsen in Iceland and by Daae in 1872 in Norway where they observed epidemics of this desease Since then, similar events have been reported from other Scandinavian countries, Germany, England, Iceland, the United States of America and New Zealand Presumably the disease is endemic on Bornholm island which lies off the coast of Denmark Thousands of cases have been observed here and in the neighboring geographic areas For this reason, the term Bornholm disease has been used in the medical literature with reference to this condition At the time when Dabney (1888) published his observations on the first known American epidemic, the popular designation of "devil s grip" was introduced It is aptly expressive of the baffling and annoying discomfort of the patient Also, the cause of the disease not having been known, it is understandable that it was conveniently attributed to the well known inhabitants of Hades who are customarily blamed for so many human evils

As its name implies, epidemic pleurodynia is a communicable disease It has been definitely established that its onset follows close contact with persons suffering from this condition Its epidemiologic aspects were studied by Nichamin (1945) on Blakely island, Mobile, Alabama As noted by previous observers, the highest incidence occurred in July and August The estimated incubation period is from one to three weeks Several members of the same family may contract the disease In other instances, only a single member of a family is affected by this condition Great variations in individual susceptibility, resistance and possible immunity account for this discrepancy In the form of epidemics, pleurodynia has been observed in certain limited groups of communities, in nurses' training schools, army camps, colleges and elsewhere Undoubtedly, in addition to epidemic outbreaks, also sporadic cases occur, although they may not be correctly diagnosed This is not surprising in view of the fact that in a great many instances, the attack is mild and symptoms and signs are of less than 24 hours' duration

Findlay and Howard and also Hopkins, demonstrated that the causative agent of this disease was one of the Coxsackie viruses

Epidemic pleurodynia is most common in children, including infants, and young adults, but it may be encountered in middle-aged and old persons Both sexes are affected with equal frequency From the

available studies, it is reasonable to assume that the virus as an etiologic factor has a highly neuorotropic tendency The severity of the disease shows great differences during various epidemics and also marked individual differences during the same epidemic Its usual duration is from one to 16 days. *Commonly, the disease is severe enough to force the patient* to bed Howard and his associates observed 166 cases during an epidemic in Brooklyn, N Y Forty of their patients were hospitalized Of this group the incidence of encephalitis was 22 7 per cent in adolescents and adults All of their patients under two years of age had generalized convulsions The reported occurrence of meningeal irritation varies greatly in different epidemics No residual changes result from these changes following recovery The incidence of plastic pleurisy is from 4 to 14 per cent This complication is apparently less frequent in the Scandinavian countries than elsewhere During an epidemic of pleurodynia in 1947, Finn and his associates observed 114 cases at the Boston (Massachusetts) City Hospital

With the exception of a small percentage of cases, the onset of the disease is sudden Most characteristic manifestations are pain and fever *The pain is stabbing, shooting sharp, excruciating in character* Its typical localization corresponds to the region of diaphragmatic attachments to the chest wall Thus the patient may complain of pain in the *lower chest, the upper abdominal quadrant, the epigastrium or the* lumbar region The pain may be unilateral or bilateral In the latter instance, its intensity is greater on one side Movements of the trunk, deep inspiration, coughing are bound to aggravate the patient s discomfort Sensory impulses may be carried through the phrenic nerve from the diaphragm to the cervical cord and from here the pain sensation is referred through the cervical cutaneous nerve to the neck, shoulder, scapula and interscapular area Transmission of pain from the diaphragm and lower portion of the chest wall to the lower abdominal quadrants may take place through the lower intercostal nerves *It is common to find pain localized simultaneously in more than one region* Recurrence of pain may follow disappearance of symptoms for from one to four days In such cases however, the pain is, as a rule, less severe than it was at the time of the first bout and it may be localized in the opposite side of the body Occasionally, pain is so severe that it interferes with normal respiration and leads to dyspnea *Rarely, the patient complains* of pain in the upper and lower extremities

The frequency of fever varies from 50 to 90 per cent of the cases Usually, it is slight or moderate, but in some patients, it may reach 105°F (40 5C) It may last less than 24 hours Often, however, it recurs with irregular periodicity Thus, it may be off and on for one or two days, or a febrile episode of three days duration is followed by normal temperature for one to four days Then fever develops again with reappearance of other symptoms Febrile temperature may be preceded by chilliness or chilly sensations or by prodromal symptoms, such as 'sore throat," or those of "upper respiratory infection"

Other symptoms noted with varying frequency include frontal headache, dizziness, fainting attacks, sensitivity to noise, photophobia, difficulty in focusing eyes on near objects, paresthesias in the extremities, such as numbness and tingling nervous irritability, heat sensation without fever, profuse perspiration, anorexia, nausea, vomiting and malaise

Diagnosis is based on the aforementioned symptoms, physical and laboratory finding and on ruling out conditions with similar clinical manifestations The pulse rate corresponds to the level of temperature Only in a few instances, has bradycardia been observed There may be a lag in the respiratory excursions on one side of the chest on account of pain and consequent splinting of the muscles Infants and children may have labored respiration with an occasional rate as high as 70 per minute Hyperesthesia and tenderness are found over the painful areas in the overwhelming majority of cases Also one may detect swelling and rigidity of muscles in the epigastrium in the upper or lower abdominal quadrants Nichamin observed that moderate palpation over the tender muscles of the upper part of the abdominal wall often provoked severe inward radiation of pain and transitory feeling of nausea Also he noted that epigastric and subcostal tenderness of muscles was present in some of his patients without localizing complaints

Restricted respiratory motions of the chest on one side result in diminished breath sounds Physical as well as fluoroscopic examinations may reveal limited motions of one hemidiaphragm Roentgenograms of the chest may suggest pulmonary congestion on the affected side These changes are brought about by the decreased respiratory excursions of the corresponding hemithorax Pleural friction sound is heard in a small percentage of cases

Symptoms and signs of meningo-encephalitis are found in these patients with varying frequency These include headache photophobia vertigo, apathy, somnolence unusual esthesia and nuchal rigidity Neuro-

logic examination may reveal positive Kernig's sign and some of the other pathognomonic signs of meningeal involvement Occasionally, haziness of the optic disk is noted McConnell reported the occurrence of signs and symptoms referable to the central nervous system in 68 1 per cent of her cases in young adults

Laboratory findings are of importance in arriving at a diagnosis The causative Coxsackie virus may be isolated from the blood, feces and nasal washings Also, specific neutralization and complement fixation tests are positive White blood cell count varies from normal to 28,000 per cubic millimeter *Occasionaly, leucopenia is found In the* differential blood count, polymorphonuclear leucocytes may reach over 90 per cent In some instances, moderate increase was recorded in the number of monocytes *Examination of the spinal fluid reveals from* slight to moderate increase in the cell count from 15 to 35 per cent of the cases, with lymphocytes predominating

There are instances on record where abdominal pain, tenderness and muscle spasm over the right upper or lower quadrant led to unnecessary laparotomies For this reason, it is mandatory to take into consideration the possibility of epidemic pleurodynia in cases of atypical acute abdominal conditions Conversely, epidemic pleurodynia should *be differentiated from acute appendicitis, cholecystitis biliary and renal* lithiasis, perforated peptic ulcer and inflammatory diseases localized in the pelvis In infants and young children, one should rule out severe pharymgitis associated with abdominal pain Other conditions which may resemble epidemic pleurodynia include influenza, acute pleurisy caused by various infections, lobar or bronchopneumonia of bacterial rickettsial or viral origin, acute rheumatism, myositis, trichinosis, infectious mononucleosis, lymphocytic choriomeningitis, nonparalytic forms of poliomyelitis and acute diaphragmitis The latter condition is discussed in detail in the chapter on *Diseases of the Diaphragm*

Prognosis is always good No death due to epidemic pleurodynia *has been recorded Convalescence is rapid* and uneventful No residual changes remain after the termination of the acute phase, except in rare instances where muscle tenderness is noted for from six to eight weeks after the onset

Nichamin observed rapid improvement following the administration of aureomycin in 74 per cent of his cases Bed rest is mandatory For the relief of pain analgesics are prescribed such as sodium *salicylate* 15 grains *(1 0 Gm) three to six times a day, with* equal amounts of

sodium bicarbonate, acetylsalicylic acid can be given in the same doses its efficacy can be improved by the simultaneous administration of small amounts of magnesium oxide, acetophenetidine (phenacetine) is administered in doses of 10 grains (0 6 Gm) three times daily Pain may be so excruciating that it necessitates the administration of narcotics morphine 1/4 grain (0 015 Gm) pantopon 1/3 grain (0 02 Gm) or dilaudid hydrochloride from 1/32 to 1/20 gr (0 002 0 003 Gm) Synthetic analgesics can be used to advantage Methadon hydrochloride is 6 dimethylamino 4 4 diphenyl 3 heptanone hydrochloride It is available in tablets of 5 7 5 and 10 mg for oral administration Also it can be given subcutaneously The latter method is preferable for the control of severe pain The usual single dose is 10 mg It may be repeated at intervals as required by the patient s condition Meperidine (isonupercaine) hydrochloride (Demerol) is available in 50 mg tablets for oral use Single dose is 100 mg The same dose is given intramuscularly Chemically meperidine is ethyl 1 methyl-4-phenylpiperidine-4-carboxylate

Intravenously given procaine is effective in relieving severe pain Five cubic centimeters of a 20 per cent solution of the drug are mixed with 1 000 cc of isotonic solution of sodium chloride and infused over a period of 20 minutes

Injection of procaine into the skin at the site of pain and tenderness is useful for relieving the patient s discomfort If necessary the injection is repeated in several hours

Pain localized in the lower part of the chest may be completely relieved by procaine block of the intercostal nerves in the corresponding area

Application of ethyl chloride spray for 20 to 30 seconds over the site of maximum pain and tenderness may bring about welcome relief

Strapping the lower part of the chest with adhesive plaster may be sufficient to alleviate the patient s condition On account of the frequency of serious skin irritation following the use of ordinary adhesive plaster it is advantageous to use stockinet adhesive recommended by Wiley as follows A piece of four inch wide tubular stockinet (such as that used about an extremity prior to the application of a plaster cast) is slightly stretched around the lower part of the patient s chest and cut off at such a length as to permit its ends to overlap about 1½ inches This piece of stockinet is then laid out straight on a flat table and with out being stretched has a strip of three inch adhesive tape stuck to its

upper surface beginning flush with one end The adhesive tape is then cut off about 10 inches beyond the opposite end of the stockinet The combination strip is then placed around the lower part of the patient's chest at the desired height with the stockinet surface next to the skin, and the free, adhesive tape end held out at a tangent to the torso The patient is instructed to inhale deeply, then exhale as completely as possible and hold that chest position until the free adhesive tape can be wrapped around the portion of the binder already in place and so stuck to the back of the stockinet end of the adhesive tape Since the stockinet extends about ½ inch beyond each side of the adhesive tape, this binder can be applied well up under female breasts without causing chafing"

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CHAPTER XXIII

DISEASES OF THE DIAPHRAGM

By Minas Joannides, M D and Minas Joannides, Jr, M D

In DISEASES of the diaphragm it is important to remember that the diaphragm because of the multiplicity of its functions is one of the very important organs of the body It is an organ that is concerned with respiration, the circulation and the digestive tract Because of its anatomical location it may be considered as a muscle which acts as the floor of the chest cavity and the roof of the abdominal cavity

Anatomy

The diaphragm is a striated muscle and has its innervation from the peripheral nervous system arising from the cervical plexus The phrenic nerve arises from the third to the fifth cervical nerves and the trunk extends down to the diaphragm The phrenic nerve receives accessory branches from the sympathetic nerve supply and brachial plexus. The accessory branches join the main trunk at various levels in the cervical region Often the accessory branches go as far down as the first or second thoracic level and occasionally find their way around the subclavian vessels The phrenic nerve gives off branches at the level of the aortic arch the hilar area, and the pericardium About two cm above its innervation to the diaphragm the nerve divides into three branches One branch extends laterally and supplies the peripheral portion of the diaphragm The second branch extends medially to the central tendon and the diaphragmatic pillars The third branch pierces the wall and supplies the under surface of the diaphragm This branch extends down to the solar plexus and the adrenal gland on each side

The Pillars of the Diaphragm

The diaphragmatic pillars are intimately related to the peripheral portion of the diaphragm and are innervated through the phrenic nerve They act as sphincter muscles to the cardiac end of the esophagus

Anatomically the pillars appear as a rounded muscular bundle which envelopes the anterior part of the esophagus and crosses the midline behind the esophagus to the opposite side to attach itself to the body of the dorso lumbar spine The pillars form the hiatus esophageus Posteriorly and behind the esophagus the hiatus is lined with areolar tissue which is the usual site of hiatal diaphragmatic hernia

Physiological Function

The pillars exert an inspiratory milking down contraction on the esophagus as well as a circular constricting effect on the esophagus. This effect can be plainly seen during a barium examination of the esophagus On inspiration, the barium is held in the cardiac portion of the esophagus and is released during the onset of expiration Experimentally a milking down contraction has been demonstrated in dogs when the index finger was inserted into the cardia through a gastrostomy These fibers may become fibrotic and cause a persistent cardiospasm Transitory cardiospasm may often be relieved by deep long breaths

Intercostal Innervation

The peripheral portion of the diaphragm has been considered as having some innervation from the intercostal nerves We found experimentally that section of the phrenic nerve caused complete atrophy of the muscle On the other hand, section of the intercostal nerves has caused paralysis and atrophy of the intercostal muscles and in the case of the lower dorsal nerves a paralysis and atrophy of the abdominal muscles At no time did we find any paralysis or atrophy of the diaphragm after section of the intercostal nerves It is safe, therefore, to assume that the diaphragm does not have any intercostal innervation

Referred Pain

During its embryologic development the diaphragm travels downward to the floor of the chest and in so doing pulls with it the trunk of the phrenic nerve Because of its cervical origin, the phrenic nerve, when irritated, causes referred pain which is elicited along the distribution of the related branches of the cervical nerves Thus any irritation of the diaphragm or the nerve trunk itself causes pain in the shoulder, the trapezius ridge, and the scalenus area

Respiratory Function

The diaphragm plays an important part in external respiration

Normally the diaphragm is dome shaped and on inspiratory contraction the dome descends by 2 to 10 cm Coincidentally the ribs are raised by the action of the external intercostals These changes result in an enlargement of the capacity of the thoracic cage Because the pleural space is a closed cavity with a pressure of —3 to —7 cm of water, an increase in the space of the chest cage causes the intrapleural pressure to become more negative, often reaching a level of—15 to—20 cm of water The only connection of the lung to the atmosphere is through the tracheobronchial tree Thus air is sucked into the tracheobronchial tree and reaches the alveoli At expiration the diaphragm relaxes to its high dome shaped position and the ribs sag down Thus the intrapleural pressure becomes less negative and air is expressed from the alveoli This process is enhanced by the contraction of the elastic tissue which is abundantly present in the lung It is well to emphasize that the respiratory exchange depends exclusively on the changes of intrapleural pressures and the inherent structure of the lung and not on mechanical pressure exerted by the relaxed diaphragm

Paralysis of the Diaphragm

Paralysis of the diaphragm assists in pulmonary relaxation so often necessary to induce healing of tuberculous pathology in the lung Such an effect may be brought about most effectively if the tonus of the diaphragmatic fibers is good enough to cause a satisfactory excursion of the muscle When the breathing is brought about primarily by costal respiration, paralysis of the diaphragm through section of the phrenic nerve cannot bring about pulmonary relaxation For this reason phrenic paralysis is inadvisable in patients who have costal type of breathing

When the diaphragm is paralyzed through section of the phrenic nerve, the muscle assumes its relaxed position There is a rise of three to ten cm higher than the non paralyzed side Furthermore, on inspiration the abdominal muscles exert a relative increase of intra abdominal pressure, thus pushing the relaxed diaphragm upward while the normal leaf contracts downward This paradoxical motion of the diaphragm has often been referred to as the *KIENBOECK PHENOMENON* This phenomenon deals with the rise of the fluid level in the chest cavity in cases of hydropneumothorax when the intrapleural pressure is sufficiently low to allow for a relative expansion of the collapsed lung The expanded lung fills up the pleural space sufficiently to cause the fluid level to rise on inspiration in spite of the contraction of the

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diaphragm We have followed this phenomenon in a case of hydropneumothorax in which the diaphragmatic area was clear of fluid and the contractions of the muscle were visible on fluoroscopic examination

Circulatory Function

The diaphragm is definitely concerned with the physiology of circulation The vena cava finds its way into the chest through the caval opening of the diaphragm The contractions of the diaphragm cause an increase in the negative pressure of the pleural cavity and allow for suction of the venous blood from the abdominal cavity into the chest and the right heart This is also true of the lymph flow through the thoracic duct

Gastro-Intestinal Function

The diaphragm bears a definite relation to gastro intestinal motility Peristaltic waves in the stomach may be initiated by the intermittent contraction and relaxation of the muscle When the diaphragm contracts the fundus of the stomach is pushed down and contracts to a greater or lesser degree Coincidentally the gastric antrum is seen to dilate Thus the contraction of the fundus and the coincidental dilatation of the antrum, with each inspiration and the opposite effect with each expiratory relaxation of the muscle, induces gastric motility The colon is also seen to travel up and down with each contraction and relaxation of the diaphragm We have noticed a diminution of the diameter of the colon with each inspiratory contraction of the diaphragm and an increase in the diameter of the colon at the expiratory relaxation of the diaphragm With the paralysis of one or the other leaf of the diaphragm certain changes in the mobility of the gastro intestinal tract become obvious When the left leaf of the diaphragm is paralyzed the fundus of the stomach becomes elevated, remains distended, and the antrum moves from side to side much like the pendulum of the clock With the rise of the fundus often a slight kink may develop at the cardia thus making the act of belching more difficult When the right leaf of the diaphragm is paralyzed the antrum is seen to be pulled more to the right side and remain immobile while the fundus contracts and expands with each respiration These findings, though present, may produce little or no complaint on the part of the patient after phrenic nerve paralysis

Relation to Abdominal Muscles

The peripheral fibers of the diaphragm have a definite anatomical relation to the fibers of the transversus abdominis muscle At the point of their attachment to the subcostal space the fibers of the two muscles interdigitate intimately before they are attached to the chest wall This anatomic relationship is of clinical and surgical significance Clinically any irritations to the muscle fibers of the diaphragm may cause irritation of the fibers of the transversus abdominis and produce clinical findings referable to the abdomen In any inflammation of the diaphragm one is apt to notice spasm of the abdominal wall Cases of acute diaphragmitis may often be mistaken for acute gallbladder pathology We have seen a patient who was subjected to an appendectomy when the real cause of his symptoms was pressure of the diaphragm produced by a tension pneumothorax

Surgically the intimate relation of the diaphragm to the transversus abdominis muscle may be utilized to reach the pleural cavity through an abdominal extra peritoneal incision for the purpose of surgical procedures in the lower lobe and especially for drainage of the pleural cavity

Spontaneous Rise of the Diaphragm

Spontaneous rise of the diaphragm may be of definite diagnostic significance Such a rise may be associated with pressure on the phrenic nerve with an eventual paralysis This may be caused by infiltrating neoplastic pulmonary lesions extending to the mediastinum It may also result from pathology of the mediastinal structures secondary to infections or neoplasms in the chest Such a finding is evidence of mediastinal pathology which may have extended from pulmonary, esophageal, or mediastinal lesions thus making them inoperable We believe that even in such cases the patient should be given the benefit of an exploratory thoracotomy in the hope of salvaging some patients who are otherwise doomed to die a miserable death from their primary lesion Contraction of the lung from fibrosis or other pathology may cause a rise of the diaphragm

Status Inspiratorius

Status inspiratorius of the diaphragm is often seen in patients with pulmonary emphysema involving the lower lobes of the lung Because of the reduced elasticity of the lung in emphysema there is a tendency for the distended alveoli to remain in that condition thus causing

pressure over the diaphragm and keeping it in the inspiratory position In such cases digital pressure upward under the costal margin with or without an abdominal support or artificial pneumoperitoneum may assist in mechanical collapse of the distended alveoli Thus the patient may be relieved of dyspnea resulting from the fixation of the diaphragm and an inadequate respiratory exchange

Hiccups

Irritative lesions in the diaphragm do not necessarily produce hiccup The clinical picture produced by such lesions will be discussed in connection with acute primary diaphragmitis A clinical and experimental study of hiccup has proven to us that the hiccup syndrome is definitely related to local lesions in the esophagus, or to central lesions in the vagus center, or along the course of the vagus nerve It is for this reason that phrenic nerve section for the relief of hiccup has proven of no value In the treatment of hiccup all efforts should be directed to the care of local esophageal lesions or lesions in the brain, especially the medullary centers

Hedblom's Syndrome

Acute primary diaphragmitis was first described by Joannides in 1935 The syndrome was named in honor of Dr Carl A Hedblom a pioneer in thoracic surgery Hedblom s syndrome is seen after chilling or acute naso-pharyngeal infections It is a primary myositis of the diaphragm It bears no relation to lesions of the diaphragmatic pleura, the lower lobes of the lung, or the subphrenic organs Lesions in these areas may follow as sequelae of Hedblom s syndrome Clinically it is manifested by the presence of an inspiratory pain in the lower chest This pain cuts short the respiratory effort and the patient stops breathing beyond a certain depth The respirations have a tendency to become costal in type There is a limitation in the expansion of the lower portion of the chest wall There is also a spasm of the abdominal muscles just below the costal margin Frequently there is pain along the upper quadrants of the abdomen but no deep tenderness The costal margin flares out and remains immobile The patient generally complains of a referred pain in the shoulder, the trapezius ridge and the supraclavicular area This pain is caused by impulses through the phrenic nerve to the cervical nerve roots associated with the phrenic and the related cervical nerves Fluoroscopically the diaphragm remains in a state of immobilization in the midposition between inspiration and expira

tion As the acute mysositis subsides the muscle fibers may be replaced by fibrous tissue and cause a flattening out of the diaphragm which has persisted for as long as 13 years after the patient s recovery from the acute symptoms The inflammation may extend to the diaphragmatic pleura and the subphrenic peritoneum thus causing complications It may be differentiated from an acute cholecystitis by the absence of tenderness over the gall bladder by the absence of a history of dyspepsia and by the symptoms referable to the irritation of the diaphragm or the phrenic nerve Acute appendicitis may be simulated by the spasm of the tranversus abdominis muscle but local tenderness over McBurney s point is usually absent In appendicitis the findings associated with Hedblom s syndrome may be present *Pleurodynia* has often been confused with Hedblom s syndrome This condition is discussed in the respective chapter Constricting pain in the intercostal spaces aggravated by breathing may also be found in *intercostal neuralgia* and *herpes zoster intercostalis* Hedblom s syndrome is a self limited disease and clears up after one to two weeks The symptoms may recur with the changes in the weather particularly with the onset of damp cold weather The treatment is symptomatic Oxygen therapy may become necessary if respiration is severely embarrassed Sedatives or even opiates may become necessary for the relief from pain Usually the coal tar analgesics have been sufficient to control the pain Diathermy has been of great help in promoting earlier recovery

Secondary Diaphragmitis

Lesions in the lower lobes of the lung or in the subphrenic areas may cause symptoms similar to Hedblom s syndrome In such cases the pre-existing primary lesion is clinically obvious

Diaphragmatic Pleurisy

In the lower lobe pathology of the lung the inflammatory process extends to the visceral pleura which in turn spreads to the parietal pleura A pleuritis of this sort results in effusion or adhesions If adhesions develop they are symptom free and are found either during a surgical dissection of the lung or at necropsy

One often hears medical men speak of pleuritic pain Our studies in the stimulation of the pleura during intra or extra pleural pneumolysis have convinced us that pain is only elicited when the intercostal nerves are irritated Manipulation of the visceral or parietal pleura has not in our experience caused any sensation or pain



Fig 1 Cross section of normal diaphragm magnified 85 times Whole thickness of diaphragm shows in section Pleural and peritoneal surfaces appear thin and without leucocytic infiltration

Fig 2 Cross section of normal diaphragm magnified 450 times Note flattened muscle fibres and absence of *leucocytic infiltration*

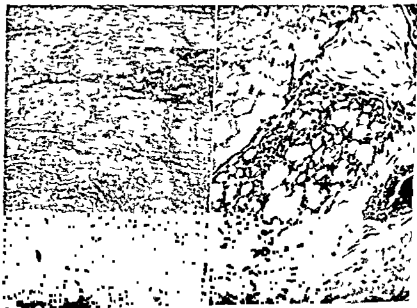




Fig 5 Acute diaphragmitis Cross section magnified 450 times Note marked swelling of muscle fibres and leucocytic infiltration between the fibers

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Fig 3 Acute diaphragmitis Cross section magnified 85 times Note swelling of muscle fibres and leucocytic infiltration between the fibres and in the lymph spaces Pleural surface thickened and unfiltrated
Fig 4 Acute diaphragmitis Cross section magnified 450 times Note leucocytic infiltration in lymph space and swelling of muscle fibres

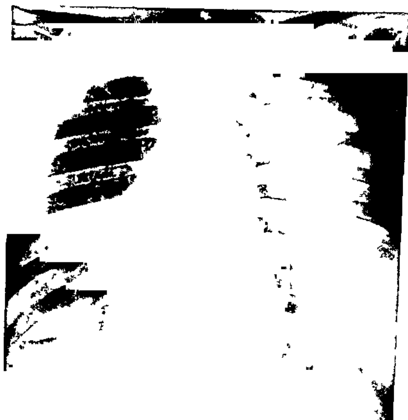


Fig 6 Roentgenogram taken on August 9 1934 It shows the definite rise of the right diaphragm There is a slight obliteration of the normal dome of the diaphragm and also a definite infiltration in the right hilum Mrs E A diagnosis Acute diaphragmitis



Fig 7 Roentgenogram taken August 14 1934 The hilar infiltration is cleared up There is a rise of the diaphragm on the right side The dome of the diaphragm is still evident Mrs E A diagnosis Acute diaphragmitis

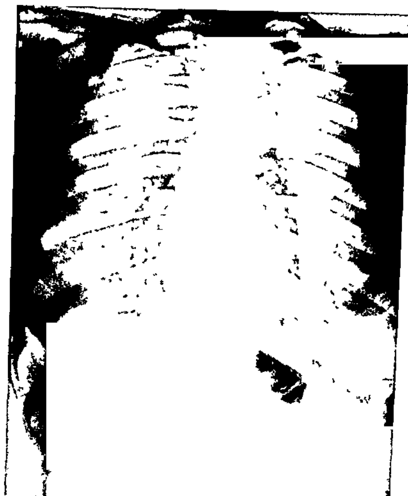


Fig 8 Roentgenogram taken September 17, 1934 The pulmonary markings show no evidence of acute pathology The dome of the diaphragm is almost entirely obliterated The costo-phrenic angle is now about 90 degrees There is a definite rise of the right hemidiaphragm Mrs E A diagnosis Recovery from acute diaphragmitis



Fig 9 Roentgenogram taken on November 17, 1934 The right hemidiaphragm is still elevated and flat Mrs E A diagnosis Recovery from acute diaphragmitis

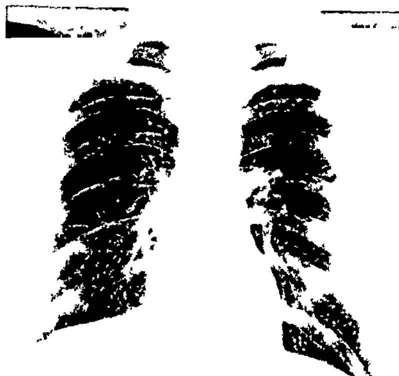


Fig 10 Roentgenogram taken September 4 1939 seven months after the acute onset The right hemidiaphragm is still high and flat Dr M S Diagnosis Recovery from acute diaphragmitis

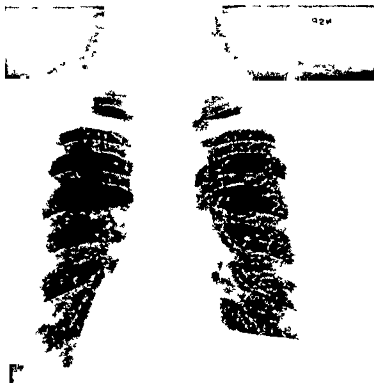


Fig 11 Roentgenogram taken September 22 1944, five years and seven months after the acute onset The right hem diaphragm is still high and shows flattening Dr M S *Diagnosis Recovery from acute diaphragmitis*

Eventration of the Diaphragm

This condition has been considered seriously a number of years ago William Lerche has described an imbrication operation to correct this condition With the popularization of diaphragmatic paralysis for the treatment of pulmonary tuberculosis we have learned not to get excited over any degree of diaphragmatic rise We frequently try to increase such a rise for added relaxation of the lung by the induction and maintenance of artificial pneumoperitoneum

Congenital Absence of the Diaphragm

This condition is rare and may be symptomless or result in death When the diaphragm is absent on one side (usually the left leaf), there is a tendency for the abdominal viscera to be pulled into the thoracic cavity If there is no tension or pull in the mesentery no symptoms may occur However, when the mesenteric vessels become strangulated and vascular changes result in the gastro-intestinal tract serious and even fatal symptoms develop Recently we saw a two day old infant who vomited constantly This baby could not hold even water A bowel obstruction was suspected and a flat film was obtained The left chest showed a number of gas bubbles which on the ingestion of a contrast meal proved to be gastric contents A diaphragmatic hernia was suspected The child died from an aspiration pneumonia on the night of the second day of observation A post mortem examination revealed a complete absence of the left leaf of the diaphragm and a strangulation of the stomach and bowel resulting from a twist in the roots of the mesentery Experimentally we removed the left leaf of the diaphragm in dogs in order to study the effects of collapse of the lung produced by the compression of intrathoracic viscera These dogs invariably died of starvation within two to three months None showed any symptoms of bowel obstruction Incidentally, the contracted lung showed no histologic change resulting from the compression collapse This finding convinced us that any fibrosis in the lung associated with pneumothorax collapse is due not to the collapse per se but the lesion for which the pneumothorax was established

Diaphragmatic Hernia

Hernia of the diaphragm may be congenital, acquired or postoperative



F g 12 Congen tal ab en e of tl e d aphragm Rad olucent area n left chest produced by an a r bubble n the stoma h

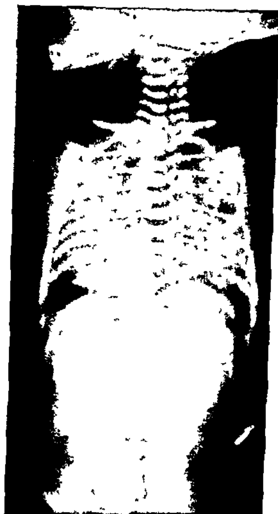


Fig 13 Congenital absence of the diaphragm Radiolucent areas showing the position of the colon in the left chest



Fig 14 Congenital absence of the diaphragm Contrast view with barium to show the stomach and bowel in the left chest.



Fig 15 Congenital absence of the diaphragm Contrast picture with barium to show the position of the bowel in the left chest

Congenital hernia of the diaphragm is generally hiatal in type The loose areolar tissue present at the hiatus esophageus between the vertebral body and the posterior wall of the esophagus is the commonest site for this type of hernia Repeated episodes resulting in increased intra-abdominal pressure cause the areolar tissue to give and result in the herniation of the stomach or the bowel into the space The sac is formed by the protrusion of the peritoneum into the hiatal space Clinically the patient may have dysphagia, substernal distress, or symptoms attributable to cardiac pathology If strangulation occurs, symptoms of acute intestinal obstruction may develop The diagnosis is established with a barium meal *Such a hernia may be repaired preferably from above* through a lower thoracic incision usually about the level of the ninth

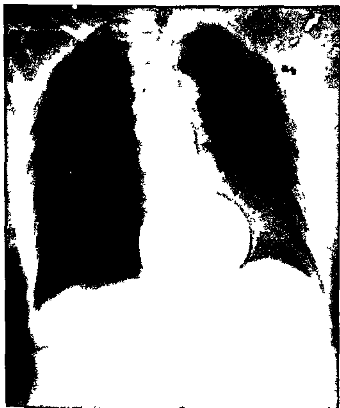


Fig 16 Hiatal hernia Contrast picture with barium to show major portion of stomach in the chest cavity



Fig 17 Congenital hiatal hernia Oblique view showing position of hernia in front of esophagus

rib or the intercostal space The hernia is reduced the sac is obliterated and the hiatal defect *is* repaired These herniae have at times been repaired through the abdominal route However the work is more difficult and the strain on the patient is greater

Traumatic hernia Is usually the result of a sudden blow to the lower chest or the upper abdomen It presents the same clinical picture as a hiatal hernia *An x ray film after a barium meal especially in a*



Fig 18 Hiatal hernia Contrast picture with barium to show relative position of the herniated stomach to the bowel

Trendelenburg position will prove the presence of the hernia The treatment consists in reduction of the hernia and the suture of the defect in the diaphragm

Postoperative hernia With the popularization of esophago-gastrostomies for esophageal carcinoma and thoraco-abdominal operations for upper abdominal lesions hernia of the diaphragm may develop if the stomach is not properly sutured to the diaphragm or the diaphragmatic opening is not properly closed If the sutures give or if they are placed too far apart a sufficiently large defect may result at the gastro-diaphragmatic junction to cause herniation of the abdominal viscera into the chest The treatment of such a complication consists of re



Fig 19 Traumatic hernia of the diaphragm Contrast picture with barium to show inverted stomach in the left pleural cavity

duction of the hernia and repair of the defect With more and more vagotomies being done the danger of diaphragmatic hernia becomes increased During the delivery of the lower end of the esophagus for the dissection of the vagi there is a tendency to loosen the attachments of the esophagus to the pillars of the diaphragm When this happens and the defect is not repaired it is possible for a hernia to develop This may be pre



Fig 20 Traumatic hernia of the diaphragm Contrast picture with barium enema to show position of the colon in the left chest cavity

ented if the esophagus is again sutured firmly to the diaphragmatic pillars

Short Esophagus

In some patients the esophagus is shorter than the full length of the chest and the cardia is not at the level of the pillars. A barium meal generally reveals an hour glass stomach at the level of the pillars. Dysphagia is the commonest symptom. At times food stagnates above the pillars and causes symptoms and signs of a peptic ulcer.

A proper diagnosis can be made through the esophagoscope by the appearance of gastric mucosa in the esophagus above the level of the diaphragmatic pillars. The condition may be corrected by cutting the diaphragmatic pillars and pulling the diaphragm to the level of the gastro-esophageal junction



Fig 21 Short esophagus Arrows point to cardia well within the chest and hour glass constriction at the hiatus esophagus

Tumors of the Diaphragm

Kirshbaum reported 12 cases of primary tumors consisting of sarcoma, myoma, fibroma, and chondroma

Secondary tumors may arise by direct extension from a primary tumor in an adjacent tissue as in the cases collected by Hedblom or from tumor emboli transported by the blood or lymph stream originating in distant organs Such tumors may cause destruction of the muscle or seriously interfere with the motility of the diaphragm Depending on the size and extent of the tumor attempts should be made to excise it if possible

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eases of the Esophagus

CHAPTER XXIV

DISEASES OF THE CHEST WALL

By Minas Joannides, M D and Minas Joannides, Jr, M D

The Chest Wall

THIS chapter will include lesions and *deformities of the chest wall* excluding those incidental to trauma Whenever possible the normal anatomical and physiologic considerations will be discussed along with *important deviations from the normal Skin lesions of the chest wall* will not be discussed in this chapter

The Bony Cage

The chest cavity is a solid air tight and water tight cavity made up of the sternum, the vertebral bodies of the dorsal spine and the ribs connecting the vertebrae with the sternum Accessory bones which deal *with the movements of the shoulder and arms are the clavicles* and the scapulae

The sternum (Breast bone) is situated in the anterior portion of the chest and serves as a solid covering to the mediastinal structures It is divided into three sections, namely the manubrium (handle), the body and the xiphoid (ensiform) process It is connected to the ribs by means of costal cartilages which make the junction more pliable The *first rib along with the sternal end of the clavicle is* joined to the sternum by means of an arthrodial joint At the lower portion of the chest *the costal cartilages of the 6th to the 11th ribs unite into a common* cartilaginous mass which joins the sternum and forms the costal margin

Among the Deviations from the Normal sternum the following *will be considered 1 Cleft sternum 2 Pigeon breast* (pectus carinatum) 3 Funnel chest (pectus excavatum "Trichterbrust")

The cleft sternum Is a developmental fissure of the sternum with or without exposure of the heart (ectopia cordis) The overlying skin

may or may not be present. Such a condition is rare It can be corrected with plastic surgery.

The pigeon breast (pectus carinatum). Is a deformity of the sternum with an increase in the antero-posterior diameter of the chest. The sternum has an increased convexity It is essentially the result of rickets which was present during the developmental stage of the bones It is usually symptomless.

The funnel chest (pectus excavatum, "Trichterbrust"). Is the result of an inward caving of the sternum This depression may be very slight or so extensive as to practically reach the vertebral column This defect is said to be due to possible congenital syphilis, fetal rickets,

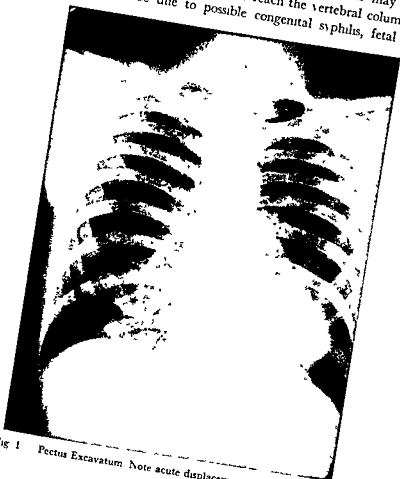


Fig 1 Pectus Excavatum Note acute displacement of heart to the left

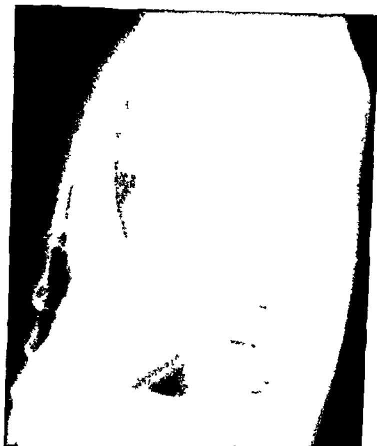


Fig 2 *Pectus Excavatum (Lateral view) Note how sternum impinges upon the heart*

hyperplasia of the thymus, or intrauterine pressure on the sternum by the child s chin knee, elbow or heel It may be symptomless or may produce pressure on the heart or cardiac displacement and produce symptoms of dyspnea, palpitation, pain and faintness. A number of surgical procedures have been described to sever the sternum from the costal cartilages and elevate it to a normal level

Absence of the xiphoid process Is a rare condition and may be associated with congenital syphilis It may be a familial manifestation and be *present in the parent and in one or more children It is more frequent* in girls than in boys

Sternal pain Often referred to as SUBSTERNAL PAIN is often a symptom for which patients seek relief It may be due to acute tracheitis or bronchitis It is often a symptom of cardiovascular disease Tenderness

of the sternum may be a manifestation of myelogenous leukemia Lesions of the mediastinum often cause pain in the substernal area

Sternal puncture Is one of the commonly used means of studying the cytologic characteristics of bone marrow It is simple and does not require any undue preparation Much of the recent progress in hema tology is the result of the use of this procedure

The Ribs

The ribs are normally 12 in number on each side They are attached posteriorly to each of the twelve dorsal vetebrae They are bent elliptically forward to join the sternum by means of a costosternal cartilage except the first rib which is attached to the sternum by means of an arthrodial joint The eleventh and twelfth ribs are floating and are not attached to the sternum On the undersurface of each rib there is a groove in which lie the intercostal vessels and nerve embedded underneath the periosteum In this way when a rib is resected if done subperiosteally, no injury will develop to the nerve or vessels The ribs are joined to each other by the intercostal muscles The fibers of the external intercostal muscles are generally directed obliquely down and medially while the internal intercostals run in the opposite direction

Among the deviations from the normal ribs The following will be considered 1 Accessory (supranumerary) ribs 2 Fusion (symphysis synostosis) of ribs 3 Surgical defects 4 Scalloping of ribs 5 Cystic disease 6 Osteoma and osteochondroma 7 Malignant tumors (pri mary and metastatatic) such as sarcoma carcinoma or myeloma 8 In fectious lesions of the ribs

Accessory (supranumerary cervical) ribs Are fairly common In a study of 180 000 x ray films of the chest we encountered this condition 33 times None of these patients complained of any distressing symp toms referable to the accessory ribs Such a condition may be unilateral or bilateral and the ribs may appear simply as a slight projection of the transerse process of the last cervical vertebra or as a definite floating rib extending into the supraclavicular space (Fig 3) When symptoms develop they are generally those of the SCALENUS SYNDROME This syn drome may be due to pressure of the accessory rib upon the brachial plexus and results in pain or paresthesia in the shoulder and the arm Relief may be obtained by the resection of the rib or by the section of the scalenus anterior muscle and in some cases all three scaleni (Adson & Coffey)

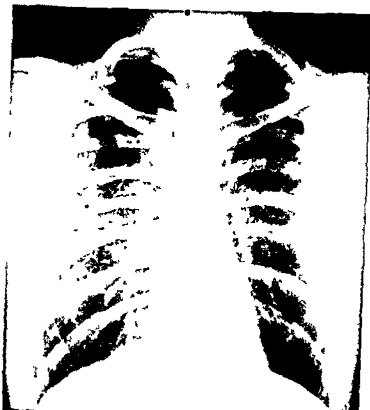


Fig 3 Cervical Rib Arrow points to anterior aspect of the accessory rib

Fusion (symphysis, synostosis) of the ribs May be congenital or acquired If it is congenital it may be associated with other bony defects (Fig 4) It may be symptomless or may cause pain or paresthesia from pressure on the related intercostal nerve If symptoms are annoying, a resection of the fused ribs with injection or section of the involved intercostal nerve will produce relief

Acquired fusion is generally the result of a subperiosteal resection of two or more ribs which subsequently regenerate in an altered position produced by the temporary softening of the chest wall during the process of regeneration of the ribs (Fig 5) A doughnut shaped fusion may often result when a subperiosteal resection of one or more ribs is done and a large drainage tube is placed in site for the drainage of empyema thoracis or persistent pleural effusions In one patient who suffered from a very annoying effusion due to an endothelioma of the pleura we maintained a closed drainage for a period of four months At



Fig 4 Congenital defects of the ribs Incomplete development of the upper three ribs Fusion of the fourth and fifth ribs Spina bifida of the lower dorsal spine

the end of that time the tube became fused within the growing bone and produced annoying pressure symptoms It became necessary to remove the regenerated rib in order to remove the drainage tube

Surgical defects of the ribs Are produced following subperiosteal resection for the purpose of collapsing the chest cavity Such a resection is based on the principle of the elimination of the rigidity of the chest wall during the process of bone regeneration from the periosteum As a result the ribs grow back in closer approximation to one another and often they are fused (Fig 5)



Fig 5 Fusion of ribs after thoracoplasty

Scalloping (notching) of ribs Is generally associated with coarctation of the aorta It is the result of increased intravascular pressure on *the intercostal vessels which act as collaterals for the stenosed aorta* This finding may be absent if there is an associated patent ductus arteriosus which may act as a shunt for the narrowed aorta When present scalloping (notching) of the rib should warrant accurate studies of the cardio-vascular system particularly with cardio angiography (Crighton Bramwell)

Benign tumors of the ribs Are not uncommon They may be *osteomata* or *osteochondromata* They do not metastasize but keep growing either outwardly or into the chest cavity (Fig 6) When they impinge upon the vessels, signs of vascular disturbance may appear on the surface *Dilatation of the superficial veins may be the first indica*tion of any If the intercostal nerves are compressed, pain or pa the patient seek relief At times

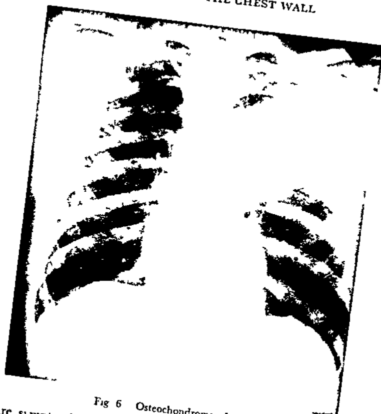


Fig 6 Osteochondroma of rib

they are symptomless and only a small superficial lump in the chest may be found accidentally and lead the patient to have a more careful study of his chest

Nodular hypertrophies of the ribs at the site of a previous fracture with displacement of the fragments may be osteomata but are called callus following a fracture



Fig 6c Osteochondroma of rib (Bucky diaphragm exposure to show detail)



g 6d Osteochomdroma of rib Appearance of chest after block removal of ribs

Cystic disease of the ribs (Solitary bulky cystic or teleangiectatic angio endothelioma) (Fig 7) is an extremely rare condition It grows steadily, perforates the shaft invades the soft parts and often produces pulmonary metastases It may pulsate and may have a bruit *Early resection with x ray radiation may produce relief*



Fig 7 Cystic disease of the rib

Malignant tumors of the ribs May be primary or metastatic SARCOMA OF THE RIB is a rather frequent primary tumor of the chest Out of 213 cases of tumors of the bony chest wall Hedblom found 131 to be sarcoma and 40 to be chondroma The cytologic characteristics of this tumor are no different than those of other bones It occurs most commonly *between 30 and 40 years and it is rare before* the age of 10 The usual symptom is pain It has a great tendency to metastasize In one of our patients the tumor which was *only about the size of a* crab

apple produced a generalized metastasis within three months and killed the patient

Metastatic tumors of the ribs are sarcomata or carcinomata Carcinoma originating from the prostate, the breast or the thyroid gland is the more common The cytologic characteristics are usually those of the primary tumor The ribs alone may be involved Most frequently they are a manifestation of a generalized skeletal metastasis of the tumor



Fig 8 Metastatic skeletal carcinoma arising from the breast

Metastatic sarcoma of the rib is usually a manifestation of generalized bony metastasis of primary sarcoma particularly of the thyroid gland or the prostate

Pathologic fractures may be the first clinical manifestation of such lesions

Multiple myeloma of the ribs (myelopathic albumosuria, 'Kahler s disease) is one manifestation of myeloma of the whole skeleton It is a rare disease It is manifested by a severe pain localized



Fig 9 Metastatic carcinoma of the ribs and skeleton originating from the prostate

over the involved bone, intermittent in character, greatly aggravated by motion and disappearing *when the body or limb is at complete rest* The pain becomes more severe and is followed with rapid loss of weight and anemia On examination the patient presents one or more tumors of cancelous portion of the ribs, spine, humerus, femur, knee and pelvis A pathologic fracture may occur during the course of the disease *Peripheral nerve lesions may develop as a result of pressure* In about 8 per cent of all cases Bence-Jones bodies may be demonstrated in the *urine or blood plasma The reaction consists of a white precipitate* formed on adding nitric acid to the urine, when boiled it disappears, to reappear on cooling It is generally fatal within two years Coley reported a case which was treated with Coley's toxin twice a week for two years and has lived for five years, to die of an acute lobar pneumonia

Infections of the ribs Are either primary or may be associated with



Fig 10 Multiple myeloma

infections of the pleural cavity or the chest wall Pyogenic infections or fungus infections particularly actinomycosis and blastomycosis may be encountered Clinically infection of the rib is manifested with all the signs of an acute localized inflammation resulting in the formation of an abscess When the abscess is incised and drained it may heal promptly or may develop a chronic draining sinus which persists for many months Osteomyelitis of the rib with sequestrum causing a persistent sinus is not as common any more since the introduction of chemotherapeutic and antibiotic agents

Tuberculosis of the rib may be observed along with tuberculosis of other bones It often follows tuberculous empyema in which repeated needling for aspiration of the chest caused the transplantation of

tubercle bacilli to the chest wall and the rib. With the use of streptomycin such a lesion is becoming more and more scarce.

The Thoracic Vertebrae

The thoracic vertebrae (dorsal) are 12 in number and all of them are attached to the corresponding ribs. Each vertebra consists of a body in the front, two laminae which are flattened plates and meet posteriorly to complete the arch and fuse at the end to produce the spinous process The hollow space (spinal foramen) produce between the laminae houses the spinal cord Each vertebra has four facets extending upward and downward to unite the vertebral pedicle and the laminae and also the vertebrae to the ribs There is a transverse



Fig 11 Kyphoscoliosis

process on each side of the vertebra to which the spinal muscles are attached and hold the vertebral column in position



Fig 11a Scoliosis with rotation of vertebrae

Deviations from the Normal

The dorsal spine Is usually straight Because of faulty posture or disease in the vertebrae curvatures may develop (Fig 11) Kyphosis results when the curvature points posteriorly Scoliosis develops when the spine curves laterally to the right or to the left Often the curvature is a combination of kyphosis and scoliosis with or without rotation of the vertebrae Usually the ribs become distorted and get crowded on the concave side and separated wider apart on the convex side Displacement of the chest organs follow the pattern of the curvature When the curvature is due to pathologic changes in the vertebrae tuberculous lesions with destruction and deformity of the vertebral body are the commonest

Infections of the dorsal spine May be acute or chronic OSTEOMYELITIS OF THE VERTEBRA although quite uncommon has been seen to develop and cause abscess The abscess unless drained promptly and treated with chemotherapy and antibiotics may cause serious deformity of the spine or extension of the infection into the spinal canal or neighboring structures Meningitis and mediastinal abscess have resulted from such extensions

Tuberculosis of the dorsal spine Is quite rare at the present time in the United States because of the elimination of the bovine tuberculosis in this country When it occurs the body of the vertebra is most often involved and when it is destroyed curvatures invariably develop

Neoplasms of the dorsal spine Are similar to those of the ribs They may be primary or metastatic They may also be benign or malignant When they are secondary to carcinoma of the prostate, recession may result by the use of large doses of estrogenic hormones When they are secondary to neoplasms of the thyroid gland radioactive isotopes may clear the lesion Bone metastases from carcinoma of the lung are generally radio resistant

The Clavicle

The clavicle (collar bone) with its attachment to the scapula gives fullness to the upper part of the chest and supports the upper extremity It is a frequent site of fracture Rarely primary tumors may develop Coley who collected 108 cases of tumors of the clavicle observed that such tumors are usually sarcomata They are more common in males than females There is a history of pain and localized swelling of the clavicle following a recent injury There is a rapid increase in the size X ray examination generally reveals osteoblastic changes and often a combination of osteoblastic and osteoclastic changes Coley reports good results after excision followed with the use of Coleys mixed toxins of erysipelas and bacillus prodigiosus

The Scapula

The scapula (shoulder blade spade) is triangular in shape and with its attachment to the clavicle and humerus forms the shoulder It is attached to the spine by means of the rhomboid muscles and to the anterior chest wall by means of the serratus anterior (serratus magnus) muscles

Winged scapula Luxation of the scapula (Figs 12 and 12a) often follows surgical procedures on the chest wall It is caused by injury to



Fig 12 Winged scapula.



Fig 12a Winged scapula.

the *long thoracic nerve* This deformity is symptomless but very unsightly The patient may get annoyed when the vertebral border of the scapula flares out with the movements of the shoulder

Drooping shoulder Elevation of the shoulder may be the result of postural changes, from lifting weights over the shoulder, and habit formation When one side droops the opposite side may appear elevated It may follow plastic operations on the chest wall for the treatment of tuberculous pulmonary lesions It may follow injury to the trapezius muscle or the brachial plexus

Tumors of the scapula Are uncommon They are generally malignant, sarcomatous in type Benign neoplasms of the scapula are usually chondromata

Subscapular abscess Is a rare condition and may be mistaken for a tumor of the chest wall or tumor of the scapula Fluctuation is demonstrable and pus may be aspirated It is rarely of tuberculous origin The pus may be sterile or contain pyogenic organisms

Subcutaneous Structures

Of the chest wall include the subcutaneous fat and areolar tissue the muscles the vessels and nerves

Lipoma of the chest wall Is quite common It may be solitary or multiple It grows slowly producing no symptoms but definite disfiguring A common site is at the spinal area and the axillary area Very frequently an accessory breast may simulate a lipoma It is usually discovered post partum when lactation develops and the mass grows rapidly in size and produces symptoms

Sebaceous cyst May develop to a sufficiently large size to become unsightly When excised, the wall of the cyst must be dissected out otherwise it will recur

Subcutaneous emphysema (interstitial emphysema) (Fig 13) Is a rather common finding It generally follows a sudden increase of the intrapulmonic pressure up to 100 mm Hg pressure This increased pressure may be instantaneous or may be prolonged It may follow a crushing injury to the chest or excessive straining as in child birth, expulsion of severely constipated feces, or as a result of anesthetic accidents The increased pressure overcomes the cohesive power of the visceral pleura especially at the area of the primary bronchus Air leaking from the alveoli finds its way through the mediastinum and the cervical fascia into the subcutaneous tissues of the neck, face, chest and arms



Fig 13 Interstitial and mediastinal emphysema Arrows point to fractured ribs Radiolucent areas show the presence of air in the subcutaneous tissues and the mediastinum The traumatic bilateral pneumothorax does not show in the picture

Interstitial emphysema may be associated with spontaneous or artificial pneumothorax, pneumoperitoneum and air embolism It is treated with multiple puncture wounds or small incision through which most of the air is squeezed out The residual air is absorbed in 7 to 20 days In order to avoid infection of the subcutaneous tissues antibiotics in adequate doses, (½ million units daily of penicillin) should be administered until the crepitation disappears

Inflammation of the muscles (myositis) May result from exposure to chilling This causes stiffening of the muscles with pain on motion One or more muscles may be involved Heat, massage, and coal tar analgesics usually give relief

Empyema necessitatis May be spontaneous and result from an empyema thoracis which is under increased pressure in the chest and



Fig 14 Subcutaneous emphysema Appearance two weeks after injury

the mediastinum is fixed It commonly is the result of aspiration of the empyema when a large needle (16 gauge) is used The puncture wound is large enough to act as a fistula to the subcutaneous tissues which have been infected during the withdrawal of the aspirating needle Incision and drainage usually results in complete healing

Atrophy of the chest muscles When unilateral is invariably due to underlying chronic pathology of the lungs Along with the atrophy the movements of the chest wall become diminished while on the opposite side they become exaggerated Muscle atrophy is a good diagnostic clue for more accurate study of the underlying structures

Intercostal and subcutaneous hematoma Is generally the result of trauma to the intercostal vessels or the vessels supplying the chest muscles or subcutaneous tissues It varies from discoloration of the skin to the point of the production of large fluctuating tumor varying

in size from a walnut to a grapefruit The aspirated fluid is bloody Incision and drainage of the hematoma results in complete healing

Intercostal neuralgia Is evidenced by attacks of pain along the course of the intercostal nerve This lesion may be due to chilling or focal infection It may be associated with lesions of the ribs or the dorsal spine which produce pressure on the nerve Removal of the cause will result in relief from the pain

The Skin

The skin of the chest wall is uniform in color and texture In highly emotional persons and also in patients suffering from hyperthyroidism a sudden momentary red flush may be seen when the patient gets upset Under very severe emotional stress PIN POINTED NAEVI may appear throughout the skin of the chest When once formed these naevi remain permanently and slowly increase in size In three to twelve months they develop into blood red sessile projections over the skin much like ' bloody warts We have noticed that persons who have such lesions usually have cardiovascular pathology As the underlying cardiovascular lesions become more advanced the skin lesions become more numerous and larger

Caput medusae thoracis Is due to dilatation of the veins of the chest wall resulting from pressure within the chest This pressure is generally associated with chest tumors compressing the mediastinal vessels and causing dilatation of the tributaries Caput medusae thoracis is a good clue for further study of lesions within the chest

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Hernia of the Lung

Definition

Hernia of the lung is a protrusion of the pleura-covered lung beyond its normal boundaries through an opening in the thoracic enclosure

Incidence

This condition is very rare To date Maurer and Blades state that less than 175 cases have been reported in medical literature This survey includes all cases reported from the American Civil War (3 cases), the Crimean War (none reported), the South African War (1 case), the Russo-Japanese War (5 cases in 20,000 wounds of the chest), World War I (none reported) A total of 171 cases were reported by Goodman in 1933

Mechanism of Production of Lung Hernia

Under physiological conditions, pressures in the chest are less than an atmosphere (negative), while in the abdomen the pressures are zero or positive Given a congenital or acquired weakness in the ab dominal structures or organs the lung may protrude through the defect In the chest cavity under similar conditions, the pressures being normally negative, the tendency would be for the lung to be kept in situ except under pathologic conditions such as persistant cough, in fact any conditions that bring about the Valsalva maneuver Under such conditions the lung may protrude through an abnormal opening in the chest wall In such a case the protruding lung may appear only at expiration or on straining

Anatomically, because the external intercostal muscles extend anteriorly to the costochondral junction a relatively weak area may develop Posteriorly the internal intercostal muscles extend only as far as the angles of the ribs, thereby resulting in a relative weakness of the wall over this area

In the dome of the chest a protrusion may occur through the superior aperture of the thorax between the scalenus anterior and the sternocleidomastoid resulting from a defect in Sibson's fascia which normally affords the necessary support When such a defect is present the expanded lung at inspiration fills in the supraclavicular space and the side of the neck, but may not produce any symptoms

The factors involved in the production of pulmonary hernia must include 1 An inherent weakness in the musculature of the chest wall

and in Sibson's fascia 2 A defect in the chest wall such as the absence of one or more ribs or a distortion of the ribs leaving a large gap between them with weakening of the intercostal muscles 3 A persistent pathologic condition in the lungs resulting in explosive and prolonged coughing 4 An injury to the chest wall or a surgical procedure as a result of which the ribs have been removed or destroyed and have not regenerated leaving a soft pliable chest wall which is drawn in at inspiration and bulges out at expiration 5 Another factor is the absence of pleuropulmonary adhesions which in time usually thicken to produce a fairly thick wall over the area

Classification of Lung Hernia

According to Morel Lavelle (1845) there are two types of classification The first type is according to location, where one may encounter (a) a cervical hernia, (b) a thoracic hernia, and (c) a diaphragmatic hernia According to etiology Morel Lavelle classified pulmonary hernia into (a) congenital, and (b) acquired, which is subdivided into (1) traumatic (2) conservative, (3) spontaneous, and (4) pathologic Such a classification is quite simple, self explanatory, and conforms with present day knowledge Exception may be made to the diaphragmatic type because of the tendency for the abdominal viscera to find their way into the chest in case of a defect in the diaphragm rather than the lung herniating into the abdomen

Symptoms

Usually there are no symptoms The patient may notice a bulge in the neck or the chest and may worry enough to seek medical advice If the defect in the chest wall is large, it may embarrass respiration

Diagnosis

Diagnosis is made by the presence of a defect in the chest wall and by the presence of a bulge at the area of the herniation when the patient strains

Treatment

In the thirty years of our practice in diseases of the chest and thoracic surgery we only have encountered three cases of pulmonary hernia Two of them were of the cervical type and presented an annoying bulge in the supraclavicular space No treatment was necessary since there were no other complaints The third one developed as a result of mass resection of the chest wall involving three ribs

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(osteochondroma) The chest wall was closed by using the pectoral muscles A hernia developed which was limited by the strength of the pectoral muscles, and which did not produce any symptoms or respiratory embarrassment Ten years after the operation the area appears the same and the patient is symptom free

If symptoms are present it may be necessary to do a plastic operation placing ribs with periosteum over the area to cover the defect Metal plates are not satisfactory and may produce complications because of the constant motion of the chest

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This Book

NONTUBERCULOUS DISEASES

OF

THE CHEST

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